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INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

GUIDELINES FOR STEM CELL SCIENCE AND CLINICAL TRANSLATION

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PREFACE

These guidelines were prepared by the ISSCR Guidelines Updates Task Force, charged with revising and updating ISSCR Guidelines for the Conduct of Human Embryonic Stem Cell Research (ISSCR, 2006) and Guidelines on the Clinical Translation of Stem Cells (ISSCR, 2008). The task force, a group of 25 scientists, ethicists, and experts in health care policy from nine countries, was chaired by bioethicist Jonathan Kimmelman. George Daley and Insoo Hyun, chairs of the guidelines task forces of 2006 and 2008, respectively, provided continuity across the three ISSCR guidelines efforts.

DEDICATION

The ISSCR dedicates these guidelines to the memory of Paolo Bianco, M.D. (1955–2015), a member of the Guidelines Update Task Force who passed away unexpectedly during the final stages of revision of these guidelines. Dr. Bianco was a professor at the Sapienza University of Rome. Throughout his distinguished career he was a pioneering stem cell researcher and leader in the effort to understand mesenchymal stem cells, a staunch defender of scientific integrity and rigor, and an esteemed colleague and mentor.

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1. FUNDAMENTAL ETHICAL PRINCIPLES

The primary societal mission of basic biomedical research and its clinical translation is to alleviate and prevent human suffering caused by illness and injury. All such biomedical research is a collective effort. It depends on the contributions of many individuals, including basic scientists, clinicians, patients, members of industry, governmental officials, and others. Such individuals often work across institutions, professions, and national boundaries and are governed by different social and cultural beliefs, regulatory systems, and expectations for moral conduct. Each may also be working toward different goals. When this collective effort works well, the social mission of clinical translation is achieved efficiently alongside the private interests of its various contributors.

Ethical principles and guidelines help secure the basis for this collective effort. Patients can enroll in clinical research trusting that studies are well justified and the risks and burdens reasonable in relation to potential benefits. Physicians and payers can be confident that the evidence they use to make important healthcare decisions is rigorous and unbiased. Private firms can invest in research programs knowing that public and institutional support will be forthcoming for the foreseeable future.

The International Society for Stem Cell Research (ISSCR)'s guidelines pertain to human stem cell research, clinical translation, and related research activities. These guidelines promote an efficient, appropriate and sustainable research enterprise for stem cell research and medical interventions that will improve human health. Guidelines do not supersede local laws and regulations. However, they can inform the interpretation and development of local laws and provide guidance for research practices not covered by legislation. The ISSCR's guidelines build on a set of widely shared ethical principles in science, research with human subjects, and medicine (Nuremberg Code, 1949; Department of Health, and Education and Welfare, 1979; European Science Foundation, 2000; Medical Professionalism Project, 2002; Institute of Medicine, 2009; World Medical Association, 2013). Some of the guidelines that follow would apply for any basic research and clinical translation efforts. Others respond to challenges that are especially applicable to stem cell-based research. These include sensitivities surrounding research activities that involve the use of human embryos and gametes, irreversible risks associated with some cell-based interventions, the vulnerability and pressing medical needs of patients with serious illnesses that currently lack effective treatments, public expectations about medical advance and access, and the competitiveness within this research arena.

Integrity of the Research Enterprise

The primary goals of stem cell research are to advance scientific understanding and to generate evidence for addressing unmet medical and public health needs. This research should be overseen by qualified investigators and coordinated in a manner that maintains public confidence and that ensures that the information obtained will be trustworthy, reliable, accessible, and responsive to scientific uncertainties and priority health needs. Key processes for maintaining the integrity of the research enterprise include those for independent peer review and oversight, replication, and accountability at each stage of research.

Primacy of Patient Welfare

Physicians and physician-researchers owe their primary duty to the patient and/or research subject. They must never unduly place vulnerable patients at risk. Clinical testing should never allow promise for future patients to override the welfare of current research subjects. Application of stem cell-based interventions outside of formal research settings should be evidence-based, subject to independent expert review, and serve patients' best interests. Promising innovative strategies should be systematically evaluated as early as possible and before application in large populations. It is a breach of professional medical ethics to market and provide stem cell-based interventions to a large patient population prior to rigorous and independent expert review of safety and efficacy.

Respect for Research Subjects

Researchers, clinicians, and clinics should empower human research participants (human subjects) to exercise valid informed consent where they have adequate decision-making capacity. This means that participants—whether in research or care settings—should be offered accurate information about risks and the state of evidence for novel stem cell-based interventions. Where individuals lack such capacity, surrogate consent should be obtained and human subjects should be stringently protected from nontherapeutic procedures that involve greater than minor increase over minimal risk. In addition, the principle of respect for research subjects should be interpreted broadly to include other entities whose interests are directly implicated by research activities, including tissue providers and researchers or their support staff who harbor conscientious objections to certain aspects of human stem cell research.

Transparency

Researchers and clinicians pursuing stem cell research should promote timely exchange of accurate scientific information to other interested parties. Researchers should communicate with various public groups, such as patient communities, to respond to their information needs, and should convey the scientific state of the art, including uncertainty about the

safety, reliability or efficacy of potential applications. Researchers and sponsors should promote open and prompt sharing of ideas, methods, data, and materials.

Social Justice
The benefits of clinical translation efforts should be distributed justly and globally, with particular emphasis on addressing unmet medical and public health needs. Advantaged populations should make efforts to share benefits with disadvantaged populations. Trials should strive to enroll populations that reflect diversity in age, sex, and ethnicity. Risks and burdens associated with clinical translation should not be borne by populations that are unlikely to benefit from the knowledge produced in these efforts. As a general rule, healthcare delivery systems, governments, insurance providers, and patients, already overburdened by rising healthcare costs, should not bear the costs of proving the safety and efficacy of stem cell-based interventions. While these parties may in some cases choose to fund clinical development, such as where there is unmet medical need and insufficient investment from the commercial sector, it is a matter of social justice that the costs of proving the safety and efficacy of a medical intervention be borne by entities that are expressly privileged to profit when such interventions are marketed. Where cell-based interventions are introduced into clinical application, their use should be linked to robust evidence development.

2. LABORATORY-BASED HUMAN EMBRYONIC STEM CELL RESEARCH, EMBRYO RESEARCH, AND RELATED RESEARCH ACTIVITIES

Stem cell research shows great promise for advancing our understanding of human development and disease. Research to address issues pertinent to the earliest stages of human development and the derivation of some types of highly versatile stem cell lines necessitates the study of human embryos.

The ISSCR holds that scientific research on preimplantation-stage human embryos is ethically permissible when performed under rigorous scientific and ethical oversight, especially in the areas of human development, genetic and chromosomal disorders, human reproduction, and new disease therapies. The ISSCR's position on the permissibility of human embryo research and the need for rigorous scientific and ethical oversight is consistent with policy statements of other organizations, most notably, the American Society for Reproductive Medicine (Ethics Committee of American Society for Reproductive Medicine, 2013), the European Society of Human Reproduction and Embryology (ESHRE Taskforce on Ethics and Law, 2001), the American College of Obstetricians and Gynecologists (2006) and the UK Human Fertilisation and Embryology Authority (2008).

This section of the guidelines pertains to:

a. The derivation of human embryonic stem cells (hESCs).

b. The banking, distribution, and preclinical use of human pluripotent stem cells.

c. The procurement of human embryos, gametes, and somatic cells for stem cell research and in vitro embryo studies not explicitly entailing stem cell derivation.

d. The in vitro and animal modeling uses of human totipotent or pluripotent cells where the experiments raise particular considerations, as outlined in greater detail below.

The guidelines in this chapter are applicable to various types of research on human embryonic cells and fetal cells, embryonic germ cells derived from fetal tissue, and research on human embryos and gametes. Institutions and investigators conducting basic research with these human biomaterials should follow the guidelines insofar as they pertain to the categories of review discussed below.

2.1 REVIEW PROCESSES

Oversight

Recommendation 2.1.1: **All research that (a) involves preimplantation stages of human development, human embryos, or embryo-derived cells or (b) entails the production of human gametes in vitro when such gametes are tested by fertilization or used for the creation of embryos shall be subject to review, approval, and ongoing monitoring by a specialized human embryo research oversight (EMRO) process capable of evaluating the unique aspects of the science. The derivation of human pluripotent stem cells from somatic cells via genetic or chemical means of reprogramming (for example, induced pluripotent stem cells or iPSCs) requires human subjects review but does not require specialized EMRO as long as the research does not generate human embryos or entail sensitive aspects of the research use of human totipotent or pluripotent stem cells as outlined in this section.**

The EMRO process encompasses oversight of human embryonic stem cell research as well as research that does not specifically entail stem cell derivation. The EMRO process can be performed at the institutional, local, regional, national, or international level or by some coordinated combination of those elements and need not be served by a single, specific committee, provided that the review process as a whole occurs effectively, impartially, and rigorously.

Currently mandated institutional reviews that assess the participation of human subjects, the procurement of human tissues in research, or the oversight for biosafety or the like may suffice as long as appropriate expertise is available to ensure that the scientific and ethical aspects of the research can be rigorously evaluated. In many cases, existing review bodies, such as the Embryonic Stem Cell Research Oversight or ESCRO committees in the U.S. (Institute of Medicine and National Research Council, 2005), are well positioned to perform review and oversight of embryo research that does not explicitly entail stem cell studies or derivation of hESC lines. A single review rather than redundant review is preferable as long as the review is thorough and is capable of addressing any uniquely sensitive elements of human embryo research and hESC research.

Review must include assessment of:

a. Scientific rationale and merit of proposal. Research with human embryos or embryo-derived 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.

b. 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 research materials. For derivation of new human embryo-derived cell lines or experiments that involve use of human embryos, relevant expertise would include prior experience with embryo culture and stem cell derivation in animal systems and competence in the culture and maintenance of human embryonic stem cells. Investigators performing derivations of embryo-derived cell lines should have a detailed, documented plan for characterization, storage, banking and distribution of new lines.

c. 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, including justification for the numbers of preimplantation embryos to be used, the proposed methodology, and for performing the experiments in a human rather than animal model system.

The mechanism or body that provides the EMRO process is responsible for interpreting the guidelines, defining research practices, and monitoring compliance. The EMRO process (a) has the responsibility for defining whether a research proposal constitutes permissible or nonpermissible research and (b) should assume responsibility for monitoring and periodic review and re-approval of ongoing research proposals.

For the derivation of iPSCs, human subjects review committees should utilize the stem cell-specific informed consent considerations discussed under Recommendation 2.2.3 and explained in detail in Appendix 1.

Composition of Research Review and Oversight Bodies

Recommendation 2.1.2: **The EMRO process should be conducted by qualified scientists, ethicists, and community members who are not directly engaged in the research under consideration.**

Participants in the EMRO process should be selected based on their relevant area-specific scientific and/or clinical expertise, ethics and research policy expertise, capacity for impartiality, and freedom from political or financial conflict regarding the research to be evaluated. Those responsible for the research review and oversight function must be cognizant of potential financial and non-financial conflicts of interest that might compromise the integrity of review. Such interest conflicts should be evaluated, minimized, and eliminated as much as possible. Each institution, academic or commercial, that engages in human embryo research shall determine an appropriate EMRO process, either internal or external, by which their researchers will be subject to independent review, approval, and monitoring of their human embryo research activities.

Recommendations for composition of participants who provide the EMRO function, addressing appropriate expertise, objectivity and responsibility:

a. 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.

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

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

d. 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.

Review Categories

Recommendation 2.1.3: **To ensure that human embryo and embryonic 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 review, research review and oversight should use the three categories of review described in this section.**

2.1.3.1 Category 1. Research that is permissible after review under existing mandates and/or committees and is determined to be exempt from the EMRO process. Category 1 research includes the following activities:

a. Research with established human embryo-derived stem cell lines that are confined to cell culture or involve routine and standard research practice, such as assays of in vitro differentiation or teratoma formation in immune-deficient mice.

b. Research that entails the reprogramming of human somatic cells to pluripotency (for example, the generation of induced pluripotent stem cells) without the creation of embryos or totipotent cells.

Institutions pursuing Category 1 research should establish an administrative 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 specialized review by an EMRO process is not required. This administrative mechanism should include a determination that the provenance of the human embryo-derived 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.

2.1.3.2 Category 2. Forms of research that are permissible only after review by an EMRO process. Comprehensive review should be coordinated with other relevant oversight, such as that provided by human subjects review committees or in vitro fertilization (IVF) clinic oversight bodies. Forms of research requiring comprehensive review by an EMRO process encompass the following activities:

a. Procurement and use of IVF embryos for research.

b. Procurement of human gametes to create research embryos.

c. Research that generates human gametes when such research entails performing studies of fertilization that produce human embryos.

d. Research involving the genetic manipulation of human embryos or gametes used to make embryos in vitro.

e. Derivation of new pluripotent cell lines from human embryos.

f. Research aimed at generating human totipotent cells that have the potential to sustain embryonic or fetal development.

g. Research involving the in vitro culture of embryos or experimental generation of embryo-like structures that might manifest human organismal potential, to ensure minimal periods of in vitro culture, as justified by compelling scientific rationale.

h. Research in which human totipotent cells or pluripotent stem cells derived by any means are mixed with human embryos.

2.1.3.3 Category 3. Prohibited research activities. Research under this category should not be pursued at this time because of broad international consensus that such experiments lack a compelling scientific rationale, raise substantial ethical concerns, and/or are illegal in many jurisdictions. Such forms of research include the following:

a. *In vitro* culture of any intact human preimplantation embryo or organized embryo-like cellular structure with human organismal potential, regardless of derivation method, beyond 14 days or formation of the primitive streak, whichever occurs first.

b. Experiments whereby human embryos or organized cellular structures that might manifest human organismal potential are gestated ex utero or in any non-human animal uterus.

c. Research in which human embryos produced by reprogramming of nuclei from somatic cells by nuclear transfer or comparable techniques are implanted into a human or animal uterus. Given current scientific and medical safety concerns, attempts at human reproductive cloning are prohibited.

d. Research in which human embryos that have undergone modification of their nuclear genome are implanted into or gestated in a human or animal uterus. Genome-modified human embryos include human embryos with engineered alterations to their nuclear DNA and/or embryos generated from a human gamete that has had its nuclear DNA modified, when such modifications will be inherited through the germ line.

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

Emerging Categories of Embryo Research That Merit Close Review

Recommendation 2.1.4: **The ISSCR supports laboratory-based research that entails modifying the nuclear genomes of gametes, zygotes and/or preimplantation human embryos, performed under a rigorous EMRO process. Such research will enhance fundamental knowledge and is essential to inform any thoughtful deliberations about the potential safety and use of nuclear genome modification in strategies aimed at preventing the transmission of genetic disorders. Until further clarity emerges on both scientific and ethical fronts, the ISSCR holds that any attempt to modify the nuclear genome of human embryos for the purpose of human reproduction is premature and should be prohibited at this time.**

Scientists currently lack an adequate understanding of the fidelity and precision of techniques for nuclear genome modification of human embryos, as well as a full appreciation of the safety and potential long-term risks to individuals born following such a process. Moreover, to date there has been inadequate public and international dialogue on the capabilities and limitations of these genome editing technologies and on the implications of their application to the human germ line. The ISSCR asserts that a deeper and more rigorous deliberation on the ethical, legal, and societal implications of modifying the human germ line is essential if clinical application is ever to be sanctioned.

In contrast, mitochondrial replacement therapy employs distinct methods and does not entail direct modification to the nuclear genome. Preclinical research into the safety and efficacy of mitochondrial replacement strategies is now underway and should continue under appropriate regulatory oversight. Thoughtful scientific and ethical discussions of this technology have recently occurred in the U.K., the U.S., and elsewhere in the world (U.K. Department of Health, 2014; National Academies of Science, Engineering and Medicine, 2016). Guidance provided by these prior reports, as well as within these guidelines provide plausible mechanisms of review, approval, and oversight of clinical translation of mitochondrial replacement therapies.

Human-animal Chimera Studies That Warrant Specialized Review

Recommendation 2.1.5: **Research that entails incorporating human totipotent or pluripotent cells into animal hosts to achieve chimerism of either the central nervous system or germ line requires specialized research oversight. Such oversight should utilize available baseline animal data grounded in rigorous scientific knowledge or reasonable inferences and involve a diligent application of animal welfare principles.**

Chimera research using human cells that have the potential for high degrees of functional integration into the animals' central nervous systems or to generate human gametes in animal hosts warrant special review (ISSCR, 2006; Academy of Medical Sciences, 2011). Institutions should determine whether chimera research involving human neural cells that have the capacity to integrate into the nervous systems of laboratory animals should be reviewed by either a specialized or pre-existing animal research review process. Specialized review processes should be triggered when the degree of functional integration is considerable enough to raise concerns that the nature of the animal host may be substantially altered and should be especially rigorous when chimerism occurs in closely related primate species. Review by animal care and use committees should be supplemented by scientists and ethicists with relevant topic-specific expertise.

To assist review and oversight of stem cell-based human-to-non-human chimera research, the ISSCR Ethics and Public Policy Committee provided an advisory report that guides reviewers through a series of considerations not typically covered by institutional animal research committees but that are relevant for review (Hyun et al., 2007). Past experiences with genetically altered laboratory animals have shown that reasonable caution might be warranted if changes carry the potential to produce new defects and deficits. Best practices today dictate that research involving modified animals must involve the following: (a) the establishment of baseline animal data; (b) ongoing data collection during research concerning any deviation from the norms of species-typical animals; (c) the use of small pilot studies to ascertain any welfare changes in modified animals; and (d) ongoing monitoring and reporting to oversight committees authorized to decide the need for protocol changes and the withdrawal of animal subjects. Findings from data collection efforts should be reported accurately and published so that others can build on them. These four steps aim to minimize unexpected distress and suffering in modified animals. Reviewers and investigators should follow the proposed ethical standards presented in the advisory report, while exercising appropriate judgment in individual situations.

2.2 PROCUREMENT OF BIOMATERIALS

The procurement of human gametes, embryos, fetal tissues, and somatic cells is integral to the conduct of human embryo and stem cell research. The international community of professional scientists engaged in human embryo and stem cell research must ensure that human biological materials are procured in accordance with globally accepted principles of research ethics and local laws and regulations.

Oversight of Procurement

Recommendation 2.2.1: **Rigorous review must be performed prior to the procurement of all gametes, embryos, or somatic cells that are destined for use in human embryo and stem cell research.**

Review by a specialized EMRO process or existing human subjects review committee bolstered by stem cell-specific expertise must ensure that vulnerable populations are not exploited due to their dependent status or their compromised ability to offer voluntary consent and that there are no undue inducements or other undue influences for the provision of human biomaterials.

Consent for Biomaterials

Recommendation 2.2.2: **Explicit and contemporaneous informed consent for the provision of all biomaterials for embryo and embryonic stem cell research is necessary, including from all gamete donors. Informed consent should be obtained at the time of proposed transfer of any biomaterials to the research team or during the time that biomaterials are collected and stored for future research use.**

Explicit and contemporaneous consent is defined as consent given by the donor at the time of procurement specifically for the use of the donor's biomaterials to derive research embryos and/or immortal stem cell lines. Explicit consent must also be given for discarded tissues and cells collected during the course of clinical practice if these biomaterials are to be used for research involving the creation of human embryos (for example, by somatic cell nuclear transfer or another method that reprograms to totipotency).

Contemporaneous consent is not necessary if researchers procure somatic cells from a tissue bank. However, somatic cells may be procured from a tissue bank for embryo or gamete research only if the tissue bank's informed consent documents specifically designate embryo or gamete creation for 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.

In the case that human biomaterials are procured from a child or a decisionally incapacitated adult, consent must be provided by a parent, legal guardian, or other person authorized under applicable law. Assent of the minor or decisionally incapacitated adult is also strongly encouraged.

Review for Biomaterials Collection for Embryo and Stem Cell Research

Recommendation 2.2.3: **Review of procurement protocols must ensure that biomaterials donors are adequately informed about the specific aspects of their voluntary research participation.**

Researchers should exercise care in obtaining informed consent. The informed consent process should take into account language barriers and the educational level of the research subjects. To facilitate the adoption of sound and uniform standards of informed consent for the procurement of biomaterials for research, the ISSCR provides template documents that can be downloaded and customized to specific protocols (Appendix 2). These sample documents will need to be customized for use in specific research studies and to conform to local laws.

If pluripotent stem cells are to be derived from procured biomaterials, the ensuing informed consent document and discussion should cover information that addresses key aspects of human stem cell research, including but not limited to the fact that an immortal stem cell line could be established that is a partial or full genetic match to the biomaterials donor and that the stem cell line could be shared with other researchers outside the institution for other research purposes that may not be fully anticipated at this time. For a list of informed consent discussion points, see Appendix 1.

Payments to Individuals Providing Tissue for Research

Recommendation 2.2.4: **Research oversight bodies must authorize all proposals to reimburse, compensate, or provide valuable considerations of any kind to providers of embryos, gametes, or somatic cells.**

Individuals who choose to provide stored biomaterials for research should not be reimbursed for the costs of storage prior to the decision to participate in research. For provision of fresh somatic cells or sperm for research, reimbursement for out-of-pocket expenses incurred by donors may be determined during the review process. For provision of embryos for research or for provision of fetal tissue, no payment or valuable consideration of any kind beyond out-of-pocket expenses may be offered to donors for their procurement.

Recommendation 2.2.5: **For provision of oocytes for research, when oocytes are collected outside the course of clinical treatment, compensation for non-financial burdens should not constitute an undue inducement.**

Because women carry more burdens than men during the procurement of their gametes, women's efforts should be acknowledged fairly and appropriately. At the same time, precaution is needed to avoid the potential for exploitation.

In jurisdictions where the provision of oocytes for research is allowed, the human subjects review committee and those responsible for conducting specialized EMRO must assess the safety and the voluntary and informed choice of women to provide oocytes for research according to the following standards:

a. There must be monitoring of recruitment practices to ensure that no socially disadvantaged individuals, for example, economically poor women, are disproportionately encouraged to participate as oocyte providers for research.

b. In jurisdictions where research subjects are allowed compensation or valuable consideration for incurred non-financial burdens, the amount of financial recognition for the subject's time, effort, and inconvenience must be rigorously reviewed to ensure that such compensation does not constitute an undue inducement.

c. Compensation for oocyte providers' time, effort, and inconvenience, if permitted by local human subjects review committees, should be reasonably consistent with recompense levels for other types of research participation involving similarly invasive and burdensome medical procedures. Compensation levels should aim to acknowledge oocyte providers' non-financial burdens incurred as a result of their research participation, such as their physical discomfort and effort.

d. At no time should payments or other rewards of any kind be given for the number or quality of the oocytes that are to be provided for research.

e. Oocyte procurement must be performed only by medically qualified and experienced physicians and frequent monitoring must be used to reduce the risk of ovarian hyperstimulation syndrome.

f. Due to the unknown long-term effects of ovulation induction, women should undergo a limited 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 a thoughtful research review and oversight process, which should be informed by the latest available scientific information about the health risks.

g. A fertility clinic or other third party responsible for obtaining consent or collecting biomaterials should not be paid specifically for the material obtained, rather for specifically defined cost-based reimbursements and payments for professional services. Fertility clinics should not profit from providing tissues for research.

To help guide review committees through the ethical considerations surrounding oocyte collection and financial recognition of providers' efforts, the ISSCR Ethics and Public Policy Committee developed an advisory report outlining their deliberations on these issues (Haimes et al., 2013).

Separating Research Consent from Treatment

Recommendation 2.2.6: **Informed consent for research donation must be kept distinct from informed consent for clinical treatment.**

To facilitate free and voluntary choice, decisions related to the provision of gametes or creation of embryos for fertility treatment should be free from influence by investigators who propose to use these biomaterials in research. During the course of clinical treatment, researchers may not request that members of the fertility treatment team generate more embryos or harvest more oocytes than necessary for the patient's optimal fertility treatment. Wherever possible, the treating physician or infertility clinician should not also be the investigator who is proposing to perform research on the procured materials.

Consistent with fetal tissue research guidelines issued by the Network of European CNS Transplantation and Restoration (NECTAR) and U.S. statute, a woman's decision to terminate a pregnancy must not be influenced by the possible research use of her fetus' tissues (Boer, 1994; OHRP, 1993). Informed consent for fetal tissue procurement and research should be obtained from the woman after her decision to legally terminate her pregnancy but before the abortive procedure. Medical procedures must not deviate from standard of care solely to facilitate the research use of donated fetal tissues. Physicians and clinics may not profit from the procurement of fetal tissues for research.

Informed Consent for Biomaterials Procurement

Recommendation 2.2.7: **The informed consent process and study design of human biomaterials procurement should be robust.**

The informed consent document is only one aspect of the informed consent 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 a dialogue between research staff and providers of human biomaterials. Researchers are thus encouraged to focus on enriching the informed consent process itself. These processes can be enhanced in the following ways:

a. 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.

b. 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 (Flory and Emanuel, 2004). Thus, researchers should provide ample opportunities for biomaterials donors to discuss their involvement in the research protocol.

c. Counseling services should be made available upon request to any providers of human biomaterials prior to procurement.

d. Consent procedures should be revised in light of research on informed consent for all types of human biological materials procurement and where relevant, ongoing studies of the long-term risks associated with oocyte retrieval.

2.3 DERIVATION, BANKING AND DISTRIBUTION OF HUMAN PLURIPOTENT STEM CELL LINES

Recommendation 2.3.1: **Proposals for derivations of new hESC lines should be scientifically justified and executed by scientists with appropriate expertise. Hand-in-hand with the privilege to perform these derivations is the obligation to distribute the cell lines to the research community.**

Although a specialized EMRO process is not required for derivation of non-embryonic stem cell lines, the general principles and aspirational goals for banking and distribution apply widely to all classes of scientifically valuable stem cell lines.

Banking in Derivation Protocols

Recommendation 2.3.2: **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.**

Consistent with the policies of many funders and scientific journals, the ISSCR encourages researchers to deposit lines early into centralized repositories where the lines will be held for release and distribution upon publication. Investigators performing derivations should have a detailed, documented plan for characterization, storage, banking and distribution of new lines. Investigators performing derivations should propose a plan to safeguard the privacy of donors. Investigators should also inform donors that, in this era of data-intensive research, complete privacy protection might be difficult to guarantee.

Incidental Findings

Recommendation 2.3.3: **Researchers and repositories should develop a policy that states whether and how incidental findings will be returned to research subjects. This policy must be explained during the informed consent process and potential subjects should be able to choose which types of incidental findings they wish to receive, if any. Reporting findings with relevance to public health may be required by law in certain jurisdictions.**

During the course of research with human stem cell lines, particularly lines derived from somatic cells, investigators may discover information that may be of importance to biomaterials donors. Because the net harms and benefits of returning incidental findings to biomaterials donors are presently unclear, a single approach to managing incidental findings may not be appropriate across all studies and jurisdictions. When studies include a plan to return incidental findings to research subjects, researchers must offer a practical and adequately resourced feedback mechanism that involves subjects' physicians and, where possible, the verification of any discovered incidental findings.

Researchers who receive materials from other researchers should be aware that they are typically prohibited from attempting to contact or identify donors with incidental findings information. Re-contact is a matter for primary research sites or central repositories to manage. However, secondary researchers should be aware of the incidental findings policies of either of these responsible parties.

For a given sample, central repositories should adhere to the incidental findings polices that were developed by the primary researchers (or others collecting biomaterials) and disclosed to donors during the informed consent process.

Successful implementation of a policy on incidental findings depends crucially on the traceability of cell line distribution. Therefore, all providers and recipients should ensure that cell lines are distributed under strict compliance with material transfer agreements.

Repositories

Recommendation 2.3.4: **The ISSCR encourages the establishment of national and international repositories that are expected to accept deposits of newly derived stem cell lines and to distribute them on an international scale.**

To facilitate easy exchange and dissemination of stem cell lines, repositories should strive to form and adhere to common methods and standards (see also Section 5, Standards in Stem Cell Research). At a minimum, each repository must establish its own guidelines and make those available to the public. Repositories must have a clear, easily accessible material transfer agreement. A sample material transfer agreement is available in Appendix 3. Each repository may have its own criteria for distribution. The repository has right of refusal if a cell line does not meet its standards. Repositories must also have clear, publicly available protocols for deposit, storage, and distribution of pluripotent stem cell lines and related materials.

For deposits, repositories must receive documentation pertinent to the depositor's applicable research review and oversight process. These documents

should be kept on file at the repository. This will include, but is not limited to, proof of 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.

Repositories 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. Repositories should make this information publicly available. If the repository modifies the depositor's protocols or obtains additional data this should also be made available.

Repositories should engage in, but are not limited to, the following:

a. Reviewing and accepting deposit applications.

b. Assigning unique identifiers (catalogue number) to deposits.

c. Characterizing cell lines.

d. Human pathogen testing.

e. Expansion, maintenance and storage of cell lines.

f. Quality assurance and quality control of all procedures.

g. Maintenance of website with pertinent characterization data, protocols and availability of cell lines.

h. Tracking distributed cell lines.

i. Posting a clear and fair cost schedule for distribution of materials. Repositories should distribute internationally and charge only the necessary costs, which include shipping and handling.

j. Adhering to an action plan, as applicable, for the return of incidental health related findings to donors.

Provenance of Stem Cell Lines

Recommendation 2.3.5: **Documentation of the provenance of stem cell lines is critical if the cell lines are to be widely employed in the research community. Provenance must be easily verifiable by access to relevant informed consent documents and raw primary data regarding genomic and functional characterization.**

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 sex, ethnicity, medical history, and infectious disease screening. Subject to local laws, donor samples and cell lines should be anonymized or de-identified. Informed consent and donor information will be gathered and maintained by the repository, including whatever reimbursement of direct expenses or financial or valuable considerations of any kind were provided in the course of the procurement.

Access to Research Materials

Recommendation 2.3.6: **Institutions engaged in human stem cell research, whether public or private, academic or nonacademic, should develop procedures whereby research scientists are granted, without undue financial constraints or bureaucratic impediment, unhindered access to 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 make best efforts 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 of cell line expansion, handling, and shipping should be borne by the receiving party so as not to pose an undue financial burden on the entity or researcher providing the cells.

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 repositories should work together to harmonize standard operating procedures to facilitate international collaboration (see also Section 5, Standards in Stem Cell Research).

2.4 MECHANISMS FOR ENFORCEMENT

Recommendation 2.4.1: **These ISSCR guidelines should be upheld and enforced through standards of academic, professional, and institutional self-regulation.**

The development of consensus in ethical standards and practices in human embryo and 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 and ethics communities. These standards and practices represent 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 embodied in these guidelines is adhered to in the course of conducting human embryo and stem cell research and of supervising junior investigators that work in their respective organizations or projects. Institutions where human embryo and stem cell research is undertaken should strive to provide 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.

Ensuring that research is performed according to scrupulous ethical standards is a legitimate concern for the peer review and editorial process of scientific publication. Journal editors and manuscript reviewers may request access to research protocols and informed consent documents to enable adequate review of the ethical framework and oversight of the research process, and may request an authors' statement of adherence to these or an equivalent set of guidelines or applicable regulations. Authors should include a statement that the research was performed after obtaining approvals following a suitable research oversight process.

Grant applicants, in particular the individual scientists undertaking the research, should provide funding bodies with sufficient documentation to demonstrate that proposed research is ethically and legally in accordance with relevant local and national regulations and these guidelines or their equivalent. Funding organizations should pledge to follow these guidelines or their equivalent and require entities whose research is funded by such organizations to do the same.

Finally, as stated previously, the ISSCR has made available for download examples of informed consent documents for obtaining human materials for research (gametes, embryos, and somatic cells) and a material transfer agreement for the sharing and distribution of materials in order to facilitate the adoption of globally accepted standards and practice of human embryo and stem cell research (Appendices 2 and 3). These templates may be modified to comply with local laws.

3. CLINICAL TRANSLATION OF STEM CELLS

This section highlights 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.

The rapid advances in basic stem cell research and the many reports of successful cell-based interventions in animal models of human disease have created high expectations for the promise of regenerative medicine and cell therapies. Accompanying the enormous attention paid by the media and the public to cellular therapies is the problematic trend towards initiation of clinical application and trials far in advance of what is warranted by sound, rigorous, and dispassionately assessed preclinical evidence. Clinical experimentation is burdensome for research subjects and expensive. Investing in a novel mode of medical intervention before there is a sound rationale, a plausible mechanism, and a high probability of success squanders limited resources and needlessly exposes research subjects to risk. This section advocates a prudent and evidence-based advance towards clinical translation. Stem cell science is best positioned to fulfill its potential by adhering to a commonly accepted and robust set of practice guidelines.

3.1 CELL PROCESSING AND MANUFACTURE

In most countries and jurisdictions, the use of cellular products for medical therapy is regulated by governmental agencies to ensure the protection of patients and the prudent use of resources so that novel therapies will be the most widely beneficial for the population. Although some cell- and stem cell-based products have now been approved for use in humans, a growing number of novel cellular products are being tested for a myriad of disease indications and present new challenges in their processing, manufacture, and pathways for regulatory approval. Given the variety of potential cell products, these guidelines emphasize that cell processing and manufacture of any product be conducted with scrupulous, expert, and independent review and oversight, to ensure as much as possible the integrity, function, and safety of cells destined for use in patients. Even minimal manipulation of cells outside the human body introduces additional risk of contamination with pathogens and prolonged passage in cell culture carries the potential for genomic and epigenetic instabilities that could lead to altered cell function or malignancy. While many countries have established regulations that govern the transfer of cells into patients, optimized standard operating procedures for cell processing, protocols for characterization, and criteria for release remain to be refined for novel derivatives of pluripotent cells and

many attendant cell therapies.

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 existing regulations. The following recommendations involve general considerations for cell processing and manufacture.

3.1.1 SOURCING MATERIAL

Donor Consent

Recommendation 3.1.1.1: **In the case of donation of cells for allogeneic use, the donor should give written and legally valid informed consent that covers, where applicable, terms for potential research and therapeutic uses, return of incidental findings, potential for commercial application, and other issues.**

Researchers should ensure that subjects or their surrogate decision-makers adequately understand the stem cell-specific aspects of their research participation. For a list of donor informed consent discussion points, see Appendix 1.

The initial procurement of tissue from a human donor may or may not require good manufacturing practice (GMP) certification depending on the jurisdiction but should always follow good laboratory practice and/or regulatory guidelines related to human tissue procurement and maintain universal precautions to minimize the risks of contamination, infection, and pathogen transmission.

Donor Screening

Recommendation 3.1.1.2: **Donors should be screened for infectious diseases and other risk factors, as is done for blood and solid organ donation, and for genetic diseases as appropriate.**

Tissue procurement for generating pluripotent cells is similar to procurement of cells for other purposes and should be governed by the same rules and regulations. However, an important distinction between tissue donation and pluripotent stem cell generation that increases the importance of screening is that, while tissues are distributed to a limited number of recipients, iPSC or other pluripotent-derived allogeneic tissues can potentially be implanted in large populations. In addition, cells are likely to be expanded in culture and/or exposed to xeno-culture materials before transplantation. As such the risk of transmission of viruses and other infectious agents such as prion particles is proportionately greater. Careful adherence to regulations and tracking of cells and the development of a risk mitigation plan is crucial to translation and uptake of cell based therapies. Regulatory agencies such as the U.S. Food and Drug Administration (FDA; http://www.fda.gov/) and the European Medicines Agency (EMA; http://www.ema.europa.eu/) have issued guidance regarding donor testing and screening.

3.1.2 MANUFACTURE

Cellular derivatives generated from tissues are considered manufactured products and are subject to various regulations. In general, current GMP protocols should be available to all researchers intending to manufacture cell products.

Quality Control in Manufacture

Recommendation 3.1.2.1: **All reagents and processes should be subject to quality control systems and standard operating procedures to ensure the quality of the reagents and consistency of protocols used in manufacturing. For extensively manipulated stem cells intended for clinical application, GMP procedures should be followed.**

The variety of distinct cell types, tissue sources, and modes of manufacture and use necessitate individualized approaches to cell processing and manufacture. The maintenance of cells in culture for any period of time places selective pressures on the cells that are different from those in vivo. Cells in culture age and may accumulate both genetic and epigenetic changes, as well as changes in differentiation behavior and function. Scientific understanding of genomic stability during cell culture and assays of genetic and epigenetic status of cultured cells are still evolving. Guidance documents from the FDA and EMA, as well as other documents, provide a roadmap for manufacture and quality control of cellular products. However, given that many cellular products developed in the future will represent entirely novel entities with difficult-to-predict behaviors, scientists must work side-by-side with regulators to ensure that the latest information is available to inform the regulatory process. An important goal is the development of universal standards to enable comparisons of cellular identity, purity and potency, which are critical for comparing studies and ensuring reliability of dose-response relationships and assessments of mechanisms of toxicity.

Processing and Manufacture Oversight

Recommendation 3.1.2.2: **The degree of oversight and review of cell processing and manufacturing protocols should be proportionate to the risk induced by manipulation of the cells, their source and intended use, the nature of the clinical trial, and the number of research subjects who will be exposed to them.**

Pluripotent stem cells carry additional risks due to their pluripotency which include the ability to acquire mutations when maintained for prolonged periods in culture, to grow and differentiate into inappropriate cellular phenotypes, to form benign teratomas or malignant outgrowths, and to fail to mature.

Appropriate tests must be devised to maximize safety of stem cell derived products.

Factors that create greater risk to recipients include the cells' proliferation and differentiation potentials, source (autologous, allogeneic), type of genetic manipulation, if any, homologous versus non-homologous or ectopic use, their persistence in the recipient, level of species specificity for cell type, and the anticipated integration of cells into tissues or organs (versus, for example, encapsulation).

When adequate cellular material is available, assays that should be applied include global and comprehensive genetic and epigenetic assessments and functional assays, as specified during review by a panel of independent experts. For cryopreserved or otherwise stored products, any impact of short- or long-term storage on product potency must be determined. Human materials associated with elevated risk (for example, allogeneic and pooled source materials) should be stringently tested for safety and quality.

When a cell-based product is claimed minimally manipulated and exempt from regulatory oversight on this basis, the onus rests on the practitioner to invite scrutiny over their process of cell manipulation, such that independent, disinterested experts can determine the proper level of regulatory oversight. Recent draft guidance provided by the FDA for public comment represents a thoughtful and cogent set of principles to delineate when manipulation of autologous cell-based products can no longer be considered minimal or their use homologous, and must therefore be subject to FDA oversight (Food and Drug Administration, 2014).

In general, the stringency of review for cell processing and manufacture should increase as cells are tested in later phase clinical studies, used in practice settings, or administered to multiple patients.

Components in Culture or Preservation of Cells

Recommendation 3.1.2.3: **Components of animal origin used in the culture or preservation of cells should be replaced with human or chemically defined components whenever possible.**

Components of animal origin are frequently highly variable, and present risks of transferring pathogens or unwanted biological material. Researchers can rebut this recommendation by demonstrating the lack of feasible alternatives and documenting favorable risk/benefit in using animal-based components.

Release Criteria

Recommendation 3.1.2.4: **Criteria for release of cells for use in humans must be designed to minimize risk from culture-acquired abnormalities. Final product as well as in-process testing may be necessary for product release and should be specified during the review process.**

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. During in-process testing, it will often be important to assess karyotypic instabilities, as well as additional global genetic and epigenetic parameters as defined by the protocol review process.

Repositories and Databases

Recommendation 3.1.2.5: **Funding bodies, industry, and regulators should work to establish public repositories and databases of clinically useful lines that contains adequate information to determine the lines' utility for a particular disease therapy.**

Some stem cell products entail minimal manipulation and immediate use, whereas other stem cell products are intended for future use and thus necessitate storage. 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 similar 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. Banks should reflect genetic diversity to promote social justice and widespread access.

Careful consideration in the design of the database must be made to promote access to appropriate individuals while restricting the release of proprietary information. As it is unlikely that any unified repository will be established, it is important to have a global nonpartisan authority along the lines of the bone marrow registry or the blood bank associations to promote harmonization of storage standards and the development of consensus standard operating procedures.

3.2 PRECLINICAL STUDIES

The purpose of preclinical studies is to (a) provide evidence of product safety and (b) establish proof-of-principle for therapeutic effects. International research ethics policies, such as the Declaration of Helsinki and the Nuremberg Code, strongly encourage the performance of animal studies prior to clinical trials. Before initiating clinical studies with stem cells in humans, researchers should have persuasive evidence of clinical promise in appropriate in vitro and/or animal models. A fundamental principle here is that preclinical studies must be rigorously designed, reported, reviewed independently, and subject to regulatory oversight prior to initiation of clinical

trials. This helps ensure that trials are scientifically and medically warranted.

Cell-based therapy offers unique challenges for preclinical studies. In many cases homologous cells in the same species are unavailable. Immune-suppressed animal models, while useful, do not permit an understanding of the effect of the immune system on transplanted cells. Since transplanted cells are considerably more complex and can change after transplantation in unpredictable ways, extrapolating cell therapies in an animal model to humans is even more challenging than for small molecule products.

3.2.1 GENERAL CONSIDERATIONS

Animal Welfare

Recommendation 3.2.1.1: **Given that preclinical research into stem cell-based therapeutics makes heavy use of animal models, researchers should adhere to the principles of the three Rs: reduce numbers, refine protocols, and replace animals with in vitro or non-animal experimental platforms whenever possible.**

This recommendation is not incompatible with performing replication experiments or achieving adequate statistical power. Indeed, these are key steps for ensuring that animal experiments support robust conclusions. This recommendation should also not be interpreted as suggesting that in vitro or non-animal platforms are sufficient for supporting clinical investigations.

Preclinical Study Objectives

Recommendation 3.2.1.2: **Early phase human studies should be preceded by rigorous demonstration of safety and efficacy in preclinical studies. The strength of preclinical evidence demanded for trial launch should be proportionate with the risks, burdens, and ethical sensitivities of the anticipated trial.**

Efficacy studies provide the scientific rationale for proceeding into human trials. More stringent design and reporting standards should be demanded where planned trials involve human research subjects with less advanced disease, when invasive delivery approaches are anticipated; or where the cell product presents greater risk and uncertainty. However, prudent use of scientific resources means that even when human research subjects have advanced disease or risk is modest, studies should rest on sound scientific evidence of expected efficacy.

Study Validity

Recommendation 3.2.1.3: **All preclinical studies testing safety and efficacy should be designed in ways that support precise, accurate, and unbiased measures of clinical promise. In particular, studies designed to inform trial initiation should have high internal validity; they should be representative of clinical scenarios they are intended to model and they should be replicated.**

Like clinical trials, preclinical experiments confront many sources of bias and confounding factors, including selection bias and publication bias. For decades, clinical researchers have sought to minimize the effects of bias and confounding by using techniques like randomized allocation, blinded outcome assessment, or power calculations. Such rigor should also apply in preclinical studies intended to support trials. Numerous groups have articulated standards for designing preclinical studies aimed at supporting trials (Fisher et al., 2009; Henderson et al., 2013; Landis et al., 2012; Kimmelman et al., 2014). Key design principles include that:

a. Researchers should reduce bias and random variation by ensuring their studies have adequate statistical power, use appropriate controls, randomization, and blinding, and, where appropriate, establish a dose-response relationship.

b. Researchers and sponsors should ensure preclinical studies model clinical trial settings. Researchers should characterize disease phenotype at baseline, select animal models that best match human disease, use outcome measures that best match clinical outcomes, and provide evidence supporting a mechanism for treatment effect.

c. Researchers and sponsors should ensure effects in animals are robust by replicating findings, ideally in an independent laboratory setting and in more than one animal model.

d. Researchers and sponsors should pre-specify and report whether a study is exploratory (i.e., hypothesis generating or aimed at substantiating basic science claims) or confirmatory (i.e., using pre-specified hypotheses and protocols and powered to support robust claims). Preclinical researchers should only venture claims of clinical utility after confirmatory studies.

3.2.2 SAFETY STUDIES

Human cells should be produced under the conditions discussed in Section 3.1, Cell Processing and Manufacture. Special attention should be paid to the characterization of the cell population, including possible contamination by unwanted cell types and to the appropriate safeguards for controlling the proliferation and/or aberrant differentiation of the cellular product. Cells grown in culture, particularly for long periods or under stressful conditions, may develop characteristics or abnormalities such as aneuploidy or DNA rearrangements, deletions, and other genetic or epigenetic changes, that could predispose them to cause serious pathologies such as tumor formation.

Cell Characterization

Recommendation 3.2.2.1: **Cells to be employed in clinical trials must first be rigorously characterized to assess potential toxicities through studies in vitro and, where possible for the clinical condition and tissue physiology to be examined, in animals.**

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 known and anticipated risks (for example, acute infusional toxicity, immune reactions, and tumor development), cell-based interventions present risks that will only be discovered with experience. As animal models may not replicate the full range of human toxicities associated with cell-based interventions, particular care must be applied in preclinical analysis. This section will define toxicities that are likely to be unique to stem cells or their progeny.

Tumorigenicity Studies

Recommendation 3.2.2.2: **Risks for tumorigenicity must be rigorously assessed for any stem cell-based product, especially if extensively manipulated in culture, genetically modified, or when pluripotent.**

The plan for assessing risks of tumorigenicity should be reviewed and approved prior to initial trials. For pluripotent stem cell-derived products, a plan needs to be in place to minimize persistence of any remaining undifferentiated cells in the final product and to demonstrate that these cells do not result in tumors in long-term animal studies.

Biodistribution Studies

Recommendation 3.2.2.3: **For all cell-based products, whether injected locally or systemically, researchers should perform detailed and sensitive biodistribution studies of cells.**

Because of the potential for cells to persist or expand in the body, systemic delivery of cells places extra burdens on investigators to understand the nature and extent by which cells distribute throughout the body, lodge in tissues, expand and differentiate. Careful studies of biodistribution, assisted by ever more sensitive techniques for imaging and monitoring of homing, retention and subsequent migration of transplanted cell populations is imperative for interpreting both efficacy and adverse events. While rodents or other small animal models are typically 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 biodistribution and toxicity of a novel cell therapy in at least one large animal model.

Additional histological analyses or banking of organs for such analysis at late time points is recommended. Depending on the laws and regulations of the specific country, biodistribution and toxicity studies may need to be performed in a good laboratory practice (GLP)-certified animal facility.

Distinct routes of cell administration, local or systemic, homologous or non-homologous/ectopic, can lead to different adverse events. For example, 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), care must be exercised in assessing the possibility of local, anatomically specific and systemic toxicities.

Ancillary Therapeutic Components

Recommendation 3.2.2.4: **Before launching high-risk trials or studies with many components, researchers should establish the safety and optimality of other intervention components, like devices or co-interventions such as surgeries.**

Cell-based interventions may involve other components besides cells, such as biomaterials, engineered scaffolds, and devices, as well as co-interventions like surgery, tissue procurement procedures, and immunosuppression. These add additional layers of risk and can interact with each other. If fully implantable devices are used, separate toxicity studies need to be carried out for the device and then separate studies will be warranted for the combo cell/device product. Many subjects in cell-based intervention studies may be receiving immunosuppressants or drugs for managing their disease. These can interact with cells. In cases where high standards of safety are demanded (for example, studies involving high risk), researchers should test their interaction.

Long-term Safety Studies

Recommendation 3.2.2.5: **Preclinical researchers should adopt practices to address long-term risks, and to detect new and unforeseen safety issues.**

Given the likelihood for long term persistence of cells and the irreversibility of some cell-based interventions, testing of the long-term effect of cell transplants in animals is encouraged and there should be stipulations in trials designed for long-term follow-up. Length of follow up should vary with survival expectancy for patient populations projected for study enrollment.

Potential of Stem Cells for Toxicology

Recommendation 3.2.2.6: **Researchers, regulators, and reviewers should exploit the potential for using stem cell-based systems to enhance the predictive value of preclinical toxicology studies.**

Stem cell science offers the prospect of testing toxicology in cell-based systems or artificial organs that more faithfully mimic human physiology than animal models. Such approaches, though unlikely to ever completely substitute for in vivo testing in animals, hold substantial promise for reducing burdens imposed on animals in safety testing and improving the predictive value of preclinical safety studies.

3.2.3 EFFICACY STUDIES

Given the therapeutic goals of stem cell-based interventions, preclinical studies should demonstrate evidence of therapeutic effect in a relevant animal model 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 critical for defining the underlying biology of the cellular therapy. However, a complete understanding of the biological mechanisms at work after stem cell transplantation is not a prerequisite to initiating trials, especially when trials involve serious and untreatable diseases for which efficacy and safety have been demonstrated in relevant animal models and/or in conclusive human studies with the same cell source.

Efficacy Evidence for Initiating Trials

Recommendation 3.2.3.1: **Trials should generally be preceded by compelling preclinical evidence of clinical promise in well-designed studies. Animal models suited to the clinical condition and the tissue physiology should be used, unless there is evidence of efficacy using similar products against similar human diseases.**

Rigorous preclinical testing in animal models is especially important for stem cell-based approaches because cell therapies have distinctive pharmacological characteristics. Before clinical testing, preclinical evidence should ideally provide the following:

a. Mechanism of action.

b. Optimal conditions for applying the cell-based intervention (for example, dose, co-interventions, delivery).

c. Ability to modify disease or injury when applied in suitable animal systems, and under conditions that are similar to expected trials (see design principles under Section 3.2.1.3, Study Validity).

d. Sufficient magnitude and durability of disease modification or injury control to be clinically meaningful.

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. However, it should be acknowledged that preclinical assays including studies in animal models may provide limited insight into variables like optimal dose or how transplanted human cells will behave in human recipients due to the context-dependent nature of cell behavior and the recipient's immune response.

In cases where a product is substantially similar to one that has already been tested in humans, trial evidence may reduce the demand for preclinical evidence.

Small Animal Studies

Recommendation 3.2.3.2: **Small animal models should be used to assess the morphological and functional recovery caused by cell-based interventions, the biological mechanisms of activity, and to optimize implementation of an intervention.**

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 can faithfully reproduce aspects of human diseases, although there are considerable limitations. Small animal studies should also use standard potency assays in an attempt to correlate cell number and potency required for large animal studies and subsequent trials.

Large Animal Studies

Recommendation 3.2.3.3: **Large animal models should be used for stem cell research when they are believed to better emulate human anatomy or pathology than small animal models and where risks to human subjects in anticipated clinical trials are high.**

Large animals may better represent human physiology as they are often genetically outbred, anatomically similar, and immunocompetent. They provide the opportunity to test co-interventions used in trials (for example, adjunctive immunosuppressive drug therapy) or the compatibility of surgical devices cell products. They also may be essential to evaluate issues of manufacturing scale up, or anatomical factors that are likely to mediate a therapeutic effect (for example, bone, cartilage, or tendon in a load-bearing model).

The need for invasive studies in non-human primates should be evaluated on a case-by-case basis, performed only if trials are expected to present high risk, and where non-human primates are expected to provide information about cell-based interventions not obtainable with other models. 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. Particular care should be taken to minimize suffering and maximize the value of studies by using rigorous designs and reporting results in full.

3.2.4 TRANSPARENCY AND PUBLICATION

Recommendation 3.2.4.1: **Sponsors, researchers, and clinical investigators should publish preclinical studies in full and in ways that enable an independent observer to interpret the strength of the evidence supporting the conclusions.**

Publication of preclinical studies serves many ends. It enables peer review of clinical research programs, thus enhancing risk/benefit ratios in trials, respects the use of animals and reagents by disseminating findings from studies, enables more sophisticated interpretation of clinical trial results, and makes possible the evaluation of preclinical models and assays, thus promoting a more effective research enterprise. However, many studies show biased patterns of preclinical publication (Sena et al., 2010; Tsilidis et al., 2013). Preclinical studies—at least those that are aimed at confirming the core principles and hypotheses underwriting a development program—should be reported in full regardless of whether they confirm, disconfirm, or are inconclusive with respect to the hypothesis they are testing. The guidelines recognize that publication may reveal commercially sensitive information and therefore acknowledge that a reasonable delay is permissible to secure appropriate protections of intellectual property. Nevertheless, preclinical studies supporting a trial should be published before the first report of trials. Animal studies should be published according to well-recognized standards, such as the ARRIVE (Animal Research: Reporting In Vivo Experiments) criteria, that have been endorsed by leading biomedical journals (Kilkenny et al., 2010).

3.3 CLINICAL RESEARCH

Clinical research, including trials of experimental interventions, is essential in translating cell-based treatments and requires participation of human subjects, whose rights and welfare must be protected. Clinical research also generates information that will be used to guide important decisions for patients, clinicians, clinical investigators, sponsors, and policy makers. The scientific integrity of this information must be safeguarded.

Sponsors, investigators, host institutions, oversight bodies, and regulators bear responsibility for ensuring the ethical conduct of clinical trials. In addition, members of the broader research community have responsibility for encouraging ethical research conduct. As with all clinical research, clinical trials of stem cell-based interventions must follow internationally accepted principles governing the ethical design and conduct of clinical research and the protection of human subjects (Department of Health, and Education and Welfare, 1979; European Parliament and Council of the European Union, 2001; World Medical Association, 1964). Key requirements include having adequate preclinical data, independent oversight and peer review, fair subject selection, informed consent, research subject monitoring, auditing of study conduct, and trial registration and reporting.

Some interventions, like assisted reproduction technologies, present challenges for standard trial designs and may be better evaluated using innovative care pathways and registries. Such approaches should nevertheless involve a pre-specified protocol, independent review for scientific merit and ethics, and a plan for reporting. Translational research on novel assisted reproductive technologies ideally combines both rigorous EMRO and human subjects review.

What follows in this section pertains to trials as well as innovative care pathways and observational studies.

3.3.1 OVERSIGHT

The overarching goal of research oversight is to ensure that a research study will likely be safe, protect human subjects, and have scientific and medical merit, and that it is designed and carried out in a manner that will yield credible data and enhance scientific and medical understanding.

Prospective Review

Recommendation 3.3.1.1: **All research involving clinical applications of stem cell-based interventions must be subject to prospective review, approval, and ongoing monitoring by independent human subjects review committees.**

Independent prospective review and monitoring is critical for ensuring the ethical basis of research with human subjects, regardless of funding source. Competent review can help minimize conflicts of interest (both financial and non-financial) that can bias research design, maximize the alignment of the goals of the research with the subjects' rights and welfare, and promote valid informed consent.

Additional independent evaluation of the research may occur through other groups, including granting agencies, peer review, embryo and embryonic stem cell research oversight bodies, and data and safety monitoring boards. Of crucial importance is that these groups collectively have the scientific, medical, and ethical expertise to conduct necessary review and oversight. To initiate stem cell-based clinical research, investigators must follow and comply with local and national regulatory approval processes.

Expert Review of Clinical Research

Recommendation 3.3.1.2: **The review process for stem cell-based clinical research should ensure that protocols are vetted by independent experts who are competent to evaluate (a) the in vitro and in vivo preclinical studies that form the basis for proceeding to a trial and (b) the design of the trial, including the adequacy of the planned endpoints of analysis, statistical considerations, and disease-specific issues related to human subjects protection.**

Peer review should also judge whether the proposed stem cell-based clinical trial is likely to lead to important new knowledge or an improvement in health. Comparing the relative value of a new stem cell-based intervention to established modes of therapy is integral to the review process. Peer review should be informed, where feasible, by a systematic review of existing evidence supporting the intervention. If decisions must be made based solely on expert opinion because no relevant literature is available, this should be described explicitly in the recommendations regarding a particular trial.

3.3.2 STANDARDS FOR CLINICAL RESEARCH CONDUCT

Systematic Appraisal of Evidence

Recommendation 3.3.2.1: **Launch of clinical trials should be supported by a systematic appraisal of evidence supporting the intervention.**

Decision-making about whether to proceed with a given research effort should be supported by a systematic review of available scientific evidence. This review should, at a minimum, consist of a synthesis of a systematic search of published studies testing the intervention in animal systems as well as unpublished studies if they are available. For early phase studies, systematic review will mostly involve synthesizing basic and preclinical investigations, while for late stage studies, systematic review should include clinical evidence. Systematic review should also be informed by accessing and synthesizing findings involving the testing of similar intervention strategies. Trial brochures should summarize the information gathered from systematic review without any bias.

Risk-Benefit Analysis

Recommendation 3.3.2.2: **Risks should be identified and minimized, unknown risks acknowledged, and potential benefits to subjects and society estimated. Studies must anticipate a favorable balance of risks and benefits.**

Efficient designs that minimize risks and include the smallest number of subjects to properly answer the scientific questions at hand should be employed. To minimize risks, eligibility criteria in prelicensure stages should be designed with consideration of potential comorbidities that may increase risk or modify the risk/benefit ratio. Correlative studies should be performed to ensure that the maximum possible information is obtained on the safety and activity of the approach being tested, provided that such assessments do not pose an undue burden for the subject.

Research Subjects Lacking Consent Capacity

Recommendation 3.3.2.3: **When testing interventions in human subjects that lack capacity to provide valid informed consent, risks from study procedures should be limited to no greater than minor increase over minimal risk unless the risks associated with the intervention are exceeded by the prospect of therapeutic benefit.**

Stem cell-based clinical trials frequently involve populations, like children or persons with advanced central nervous system disorders, who may lack capacity to provide valid informed consent. Because such individuals cannot protect their own interests, they require extra protection from research risk. This recommendation pertains to risks that lack a therapeutic justification, for example, tissue biopsies to test biodistribution, sham procedures, or withdrawal of standard treatments to monitor response during unmedicated periods. Such procedures should not exceed minor increase over minimal risk when trial populations lack capacity to provide valid informed consent. In addition, in this setting, assent of the research subject should be obtained where possible. Because definitions of minimal risk vary by jurisdiction, researchers should adhere to policies defined by local human subjects review committees, or otherwise consider minimal risk as "risk that is no greater than that associated with routine medical or psychological examination."

The issue of obtaining informed consent and/or assent from children for research is not unique to stem cell research. Accordingly, research conducted with children should adhere to recognized ethics and legal standards for this research.

Objectives of Trials

Recommendation 3.3.2.4: **A stem cell-based intervention must aim at ultimately being clinically competitive with or superior to existing therapies or meet a unique therapeutic demand. Being clinically competitive necessitates having reasonable evidence that the nature of existing treatments poses some type of burden related to it that would likely be overcome should the stem cell-based intervention prove to be safe and effective.**

Subject Selection

Recommendation 3.3.2.5: **Individuals who participate in clinical stem cell research should be recruited from populations that are 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. Unless scientifically inappropriate, trials should strive to include women as well as men and members of racial and/or ethnic minorities.**

Well-designed clinical trials and effective stem cell-based therapies should be accessible to patients without regard to their financial status, insurance coverage, or ability to pay. In stem cell-based clinical trials, the sponsor and principal investigator should make reasonable efforts to secure sufficient funding so that no person who meets eligibility criteria is prevented from enrollment because of his or her inability to cover the costs of participation.

Given current scientific understanding, a rational justification might be made to exclude pregnant women from clinical stem cell research given the potential risk to the fetus. Similarly, assuming that a particular condition is not thought to adversely affect decision making capacity, clinical research should generally seek to enroll those who have a capacity to provide consent rather than those who are unable. However, such decisions should be revisited as more is learned about such risks and the benefits of particular interventions. When conducting late phase or post-approval trials, investigators should generally plan, design, analyze, and report trials to examine relationships between treatment response and sex/gender, race, or ethnicity.

Informed Consent

Recommendation 3.3.2.6: **Informed consent must be obtained from potential human subjects or their legally authorized representatives. Reconsent of subjects must be obtained if substantial changes in risks or benefits of a study intervention or alternative treatments emerge over the course of the research.**

Culturally appropriate, voluntary informed consent is a necessary component in the ethical conduct of clinical research and the protection of human subjects. Subjects should be made aware that their participation is voluntary and not necessary for their continued clinical care, and that participation or non-participation will not interfere with their ongoing clinical care. In addition, consent discussions should emphasize that once the therapy is given it cannot be removed and that subjects must be free to withdraw consent without penalty. Specific consent challenges in early phase trials are discussed below.

Assessment of Capacity to Consent

Recommendation 3.3.2.7: **Prior to obtaining consent from potential adult subjects who have diseases or conditions that are known to affect cognition, their capacity to consent should be assessed formally.**

Subjects who lack decision making capacity and the medical conditions that can adversely affect decision making capacity should not be excluded from potential biomedical advances involving stem cells. At the same time, patients who lack capacity should be recognized as especially vulnerable. As permissible by law, steps should be taken to involve guardians or surrogates who are qualified and informed to make surrogate research judgments and to provide other protections for them. See also Recommendation 3.3.2.3.

Privacy

Recommendation 3.3.2.8: **Research teams must protect the privacy of human subjects.**

Privacy is an important value in many settings. Moreover, there are longstanding professional obligations to maintain confidentiality in medical care and research. Given the high profile of many stem cell-based intervention trials, it is particularly important for research teams to take steps to protect the privacy of research subjects. For instance, research data should be maintained in a secure manner with access restricted to study staff, oversight bodies, and agencies who have a legitimate right to review these data.

Patient Sponsored and Pay to Participate Trials

Recommendation 3.3.2.9: **Patient-sponsored and pay-to-participate trials pose challenges for ensuring scientific merit, integrity, and priority as well as fairness. Accordingly, these financial mechanisms should be used only if they are approved and supervised by a rigorous independent review body that espouses the principles outlined in these guidelines regarding integrity of the research enterprise, transparency, and patient welfare.**

Patients can be involved in the financing of trials in at least two major capacities. In patient sponsored trials, patients provide funding for research efforts in general, often through foundations or other independent entities. In pay-to-participate trials, an individual patient pays to enroll in research or otherwise receive an experimental stem cell-based intervention.

Patient-sponsored trials present opportunities for individual or groups of patients to directly engage in the research process and fund work that public and industry sponsors are unwilling to undertake. Nevertheless, they present ethical and policy challenges. Patient sponsors may press for study designs that eliminate elements such as randomization to a comparator arm and eligibility criteria that are critical for promoting scientific validity and patient welfare. Patient sponsors may also lack the expertise to distinguish meritorious protocols from those that are scientifically dubious. Further, there may be confusion over the intellectual property rights associated with successful interventions. Finally, patient-sponsored trials may divert resources such as study personnel from research activities that advance more promising research avenues.

Pay-to-participate trials raise similar concerns regarding the responsible design and conduct of research. However, whereas patient groups may have a strong research orientation, individual patients seeking trial access may not. Consequently, patient payers may press for studies that are poorly justified or not well designed. By potentially coopting research teams from pursuing research endeavors that have received support through more traditional peer reviewed mechanisms, this may unfairly disadvantage patients who lack the resources to set research agendas. Pay-to-participate research also raises questions of selection bias given that only those with access

to resources may be able to enroll in trials. Finally, because patients transact directly with those offering trial participation, direct payment for participation supports a business model whereby patients might be charged for receiving unproven and ineffective stem cell-based interventions.

The potential liabilities of patient-sponsored and pay-to-participate research should be managed by requiring that protocols considering the use of such arrangements undergo independent expert review for scientific rationale, priority and design. While input from patient communities can greatly enhance the research process, independent oversight is essential to ensure the responsible conduct of research and its reporting.

3.3.3 ISSUES PARTICULAR TO EARLY PHASE TRIALS

Early phase trials provide the first opportunity to evaluate methods and effects of promising stem cell-based interventions in humans. It also represents the first occasion where humans are exposed to an unproven intervention. Because early phase studies of stem cell-based interventions involve high levels of uncertainty, investigators, sponsors, and reviewers may have very different views about the adequacy of preclinical support for trial initiation.

Consent in Early Phase Trials

Recommendation 3.3.3.1: **Consent procedures in any prelicensure phase, but especially early phase trials of stem cell-based interventions, should work to dispel potential research subjects' overestimation of benefit and therapeutic misconception.**

Early phase trials involving stem cell-based interventions may enroll research subjects who have exhausted standard treatment options. In some cases, trials enroll individuals who have just experienced a life-altering medical event. Such individuals may be prone to overestimating the likelihood or degree of benefit of the experimental intervention ("therapeutic mis-estimation"), overlooking the implications of study participation, or mistaking demarcated research procedures for therapeutic ones ("therapeutic misconception"). Accordingly, investigators should make particular efforts to ensure that informed consent is valid in this setting. Approaches that might be considered include:

a. Conducting informed consent discussions that include a discussant who is independent of the research team.

b. Explaining to prospective subjects that major therapeutic benefits in early phase studies are exceedingly rare.

c. Testing prospective subjects on comprehension before accepting their consent

d. Requiring a "cooling off" period between provision of consent discussions and acceptance of consent.

e. Avoiding language that has therapeutic connotations, for example, using words like agent or cells rather than therapy.

f. Supplementing consent forms with additional educational materials.

Resources for drafting consent forms in early phase trials can be found at the National Institutes of Health Office of Biotechnology Activities (National Institutes of Health, 2014).

Pacing of Testing

Recommendation 3.3.3.2: **In general, initial tests of a novel strategy should be tested under lower risk conditions before escalating to higher risk study conditions even if they are more likely to confer therapeutic benefit.**

The approach of risk escalation enables researchers to refine and test techniques before advancing towards more aggressive strategies. It also helps to minimize the prospect of catastrophic events that might undermine confidence in development in stem cell-based interventions. Investigators should generally begin at lower doses, use less risky delivery procedures, use less aggressive co-interventions, and stagger testing. Staggered testing provides the opportunity to carefully review experiences and results prior to posing risk to additional subjects. Researchers should, in general, validate safety and techniques in research subjects with advanced disease before testing their products in research subjects with more recent disease onset. There may nevertheless be situations where, because of delivery or disease target, a cell product is not suitable for initial evaluation in individuals with advanced disease.

Maximizing Value

Recommendation 3.3.3.3: **Researchers should take measures to maximize the scientific value of early phase trials.**

Many interventions tested in early phase trials do not eventually show safety and efficacy. However, even unsuccessful translation efforts return a wealth of information for developing stem cell-based interventions. Early phase researchers should take several steps to maximize what is learned in early phase trials. First, where possible they should design studies that identify dose effects and mechanisms of action. These help researchers to determine whether cells have reached or engaged their targets. Second, they should seek to use standardized assays, endpoints, and methods. This enables researchers to synthesize results from individual, statistically underpowered trials (see Recommendation 5.1). Third, researchers should publish trials, methods, and sub-analyses in full. Studies show that many aspects

of early phase studies are incompletely reported (Camacho et al., 2005; Freeman and Kimmelman, 2012). Last, where resources permit, researchers should bank tissues and/or approach research subjects or families for permission to perform an autopsy in the event of death (see also Recommendation 3.3.5.3).

3.3.4 ISSUES PARTICULAR TO LATE PHASE TRIALS

Late phase trials are aimed at providing decisive evidence of clinical utility. They do this by using clinical measures of benefit, typically in larger numbers of participants, and by monitoring response over a longer, more clinically relevant period. To protect the ability to draw valid conclusions about clinical benefit, late phase trials generally use randomization and comparator arms. The choice of comparator presents some distinctive ethical challenges in the context of stem cell-based interventions.

Choice of Comparators

Recommendation 3.3.4.1: **Clinical research should compare new stem cell-based interventions against the best therapeutic approaches that are currently or could be made reasonably available to the local population.**

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 on the quality of care available locally. Trials should not be conducted in a foreign country solely to benefit patients in the home country of the sponsoring agency. Similarly, trials should not be conducted in a foreign country solely due to lack of or less stringent regulation. 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. In addition, research should be responsive to the health needs of the country in which it is conducted. For example, clinical trials with comparator arms should compare new stem cell-based interventions against best therapeutic approaches that are currently available to the local population.

Placebo and Sham Comparators

Recommendation 3.3.4.2: **Where there are no proven effective treatments for a medical condition and stem cell-based interventions involve invasive delivery, it may be appropriate to test them against placebo or sham comparators, assuming early experience has demonstrated feasibility and safety of the particular intervention.**

If early phase trials appear to demonstrate safety and efficacy, there may be compelling scientific reasons to justify a placebo or sham arm in later stage trials. In all such cases, the choice of a control arm should be explicitly justified.

Rigorous and internally valid evaluations of stem cell-based interventions may require randomized trials in which sham procedures are employed as comparators. However, sham procedures are burdensome for subjects and have no direct benefit for them. Use of sham comparators is only appropriate when they are crucial for the study's internal validity, when the study is adequately powered, and where researchers have minimized burdens by using the least invasive sham option available. In addition, researchers should ensure that the validity advantages of sham procedures are not undone by protocol flaws, for example, factors that could unblind research subjects or investigators. Regardless, placebo or sham procedures must be sensitive to the clinical context and pose no more than minimal incremental risk, i.e., risk that is minimally increased in proportion to the total risks presented to subjects by participation in the trial.

Researchers should take particular care explaining the use of placebos or sham procedures during the informed consent process and ensure patients understand and agree that they may receive a treatment with no anticipated clinical benefit.

3.3.5 RESEARCH SUBJECT FOLLOW-UP AND TRIAL MONITORING

Data Monitoring

Recommendation 3.3.5.1: **An independent data-monitoring plan is required for clinical studies. When deemed appropriate, aggregate updates should be provided at predetermined times or on demand. Such updates should include adverse event reporting and ongoing statistical analyses if appropriate. Data monitoring personnel and committees should be independent from the research team.**

The risk/benefit balance can change over the course of clinical research, as safety and response is observed, recruitment wanes, or as new treatments become available. This is especially true for stem cell-based intervention trials, which are characterized by high uncertainty and rapidly evolving science. The welfare of subjects must be carefully monitored throughout the duration of stem cell-based clinical trials, the study interrupted if the risk/benefit balance becomes unfavorable, and subjects informed of new information about themselves, the trial, or the intervention that might materially affect their continued participation in a study.

Long-term Follow-up

Recommendation 3.3.5.2: **Given the potential for transplanted cellular products to persist, and depending on the nature of the experimental stem cell-based intervention, subjects should be advised to undergo long-term health**

monitoring. Additional safeguards for ongoing research subject privacy should be provided. Subject withdrawal from the research should be done in an orderly fashion to promote physical and psychological welfare.

Long-term follow-up provides an opportunity to monitor the emergence of late adverse events and the durability of benefit. Given the practical realities, conducting long-term follow-up may be challenging. Investigators should develop and adopt measures to maintain contact with research subjects. In addition, funding organizations should be encouraged to develop mechanisms for supporting long-term follow-up. Since the length of appropriate follow-up is impossible to specify in the abstract, the decisions about this should be clearly articulated by investigators and reviewed by independent peer-reviewers and oversight bodies.

Autopsy

Recommendation 3.3.5.3: **To maximize the opportunities for scientific advance, research subjects in stem cell-based intervention studies should be asked for consent to a partial or complete autopsy in the event of death to obtain information about cellular implantation and functional consequences. Requests for an autopsy must consider cultural and familial sensitivities. Researchers should strive to incorporate a budget for autopsies in their trials and develop a mechanism to ensure that these funds remain available over long time horizons if necessary.**

Though a delicate issue, access to post mortem material substantially augments the information coming out of trials and enables future product or delivery refinements in the treated condition. Since consent for autopsy is typically obtained from the family members of someone who has died, investigators should facilitate discussion of this issue among subjects and appropriate family members well ahead of any predictable terminal event.

3.3.7 TRANSPARENCY AND REPORTING OF RESEARCH RESULTS

Registration

Recommendation 3.3.7.1: **All trials should be prospectively registered in public databases.**

Registration offers transparency regarding promising stem cell-based interventions, so that patients, regulators and the scientific community can monitor these efforts and incorporate them into future efforts, thereby minimizing risk and maximizing benefits of clinical trials. In addition, registration promotes access to clinical trials for patients who might not otherwise have a means of knowing about them.

Adverse Event Reporting

Recommendation 3.3.7.2: **Investigators should report adverse events including their severity and their potential causal relationship with the experimental intervention.**

Knowing the safety profile of stem cell-based interventions is critical for effective translation. Timely analysis of safety information is also crucial for reducing the uncertainties surrounding stem cell-based interventions. Unfortunately, many studies report deficiencies in adverse event reporting for novel therapeutics (Saini et al., 2014). Researchers should report adverse events associated with cells, procedures, and all other aspects of the intervention. When relevant, researchers should also actively report the absence of serious or fatal adverse events.

Publication

Recommendation 3.3.7.3: **Researchers should promptly publish aggregate results regardless of whether they are positive, negative or inconclusive. Studies should be published in full and according to international reporting guidelines.**

Publication of all results and analyses, regardless of whether an agent is advanced to further translation or abandoned, is strongly encouraged to promote transparency in the clinical translation of stem cell-based therapies, to ensure development of clinically effective and competitive stem cell-based therapies, to prevent individuals in future clinical trials from being subjected to unnecessary risk, and to respect research subjects' contribution. As such, reporting must be timely and accurate. Researchers should also consider ways to share individual research subject data, provided adequate privacy protections for research subjects can be assured. A recent U.S. Institute of Medicine Report offers principles on sharing clinical trial data (Institute of Medicine, 2015). Researchers, sponsors, and others should adhere to these principles.

If the particular project can be described according to internationally recognized reporting guidelines, this format should be used. For example, researchers should report all randomized trials according to the CONSORT statement recommendations (Consolidated Standards of Reporting Trials; http://www.consort-statement.org/). Journal editors should accommodate publication of inconclusive and disconfirmatory findings. See also Section 4, Communications.

3.4 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. Stem cell-based products typically entail complex manufacturing protocols and stem cell-based mechanisms of tissue repair and regeneration require considerable scientific expertise to exploit for clinical benefit. Consequently, clinical success with stem cell-

WARNING ON THE MARKETING OF UNPROVEN STEM CELL-BASED INTERVENTIONS

The ISSCR condemns the administration of unproven stem cell-based interventions outside of the context of clinical research or medical innovation compliant with the guidelines in this document and relevant laws, particularly when it is performed as a business activity. Scientists and clinicians should not participate in such activities as a matter of professional ethics. For the vast majority of medical conditions for which putative "stem cell therapies" are currently being marketed, there is insufficient evidence of safety and efficacy to justify routine or commercial use. Serious adverse events subsequent to such procedures have been reported and the long-term safety of most stem cell-based interventions remains undetermined. The premature commercialization of unproven stem cell treatments, and other cell-based interventions inaccurately marketed as containing or acting on stem cells, not only puts patients at risk but also represents one of the most serious threats to the stem cell research community, as it may jeopardize the reputation of the field and cause confusion about the actual state of scientific and clinical development. Government authorities and professional organizations are strongly encouraged to establish and strictly enforce regulations governing the introduction of stem cell-based medical interventions into commercial use.

based interventions is highly unlikely to follow from a merely empirical approach and thus, as a rule, stem cell-based products should rarely if ever be developed outside of a formal clinical trials process. Nonetheless, 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 seriously ill patients. Such limited attempts at medical innovation contrast with the marketing of unproven stem cell interventions noted in Section 3.4, Stem Cell-based Medical Innovation and Sidebar, Warning on the Marketing of Unproven Stem Cell-based Interventions.

In the case of medical innovations using stem cells and their direct derivatives, unique considerations justify a heightened level of caution. The diseases that potentially could be targeted by stem cell-based interventions are some of the most intractable ones 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 (Lau et al., 2008; Hyun, 2013). Due to their relative novelty in science, stem cells and their direct derivatives may behave more unpredictably when delivered to patients than either drugs used off-label or modified surgical techniques. 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 (Munsie and Hyun, 2014).

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 review 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 research subject protections. This is especially true when stem cell-based medical innovation provided to a small number of patients is considered promising enough to be applied to larger numbers of patients. At this critical stage of discovery and refinement of clinical practice, it is incumbent upon the practitioner to invite scrutiny by external experts in the form of peer review, institutional oversight, and presentation of observations and data in peer-reviewed medical publication so that the knowledge can benefit all.

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. Given the experimental and highly uncertain nature of such interventions, providers should under no circumstances promote, advertise, attempt general recruitment of patients, or commercialize such interventions. If the goal is to develop generalizable knowledge, such interventions should be made the subject of a controlled, registered clinical trial. Approval for marketing and reimbursement should remain conditional upon the completion of clinical investigations that demonstrate safety and efficacy, as judged by rigorous independent expert regulatory review.

Provision of Innovative Care

Recommendation 3.4.1: **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 and according to the highly restrictive provisions outlined in this section.**

These provisions include, 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 3.1, Cell Processing and Manufacture.
    iv. Description of how the cells will be administered, including adjuvant drugs, agents, and surgical procedures.
    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 patient is not eligible for an existing stem cell-based trial for this indication.
d. The clinical and administrative leadership of the healthcare institution supports the decision to attempt the medical innovation and the institution is held accountable for the innovative procedure.
e. 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.
f. Voluntary informed consent is provided by patients who appreciate that the intervention is unproven and who demonstrate their understanding of the risks and possible benefits of the procedure.
g. There is an action plan for adverse events that includes timely and adequate medical care and if necessary psychological support services.
h. Insurance coverage or other appropriate financial or medical resources are provided to patients to cover any complications arising from the procedure.
i. 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).
    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 the hopes of patients, undermine public trust in stem cell research, and unnecessarily delay rigorous clinical trials. Strict application of the above criteria to many such 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.

3.5 CLINICAL APPLICATION

Clinical translation continues after a product is taken up in clinical practice. Realizing the full potential of a product requires gathering additional safety and efficacy evidence, controlling applications that lack solid evidentiary footing, and pricing products in a way that delivers value for patients and healthcare systems.

3.5.1 REGULATORY APPROVAL

Recommendation 3.5.1.1:The **introduction of novel products into routine clinical use should be dependent on the demonstration of an acceptable balance of risk and clinical benefit appropriate to the medical condition and patient population for which new treatments are designed.**

Regulatory approval represents a key pivot point in a product's translation. National governments and regulatory authorities should maintain rigorous review pathways to ensure that stem cell-based products conform to the highest standards of evidence-based medicine.

Even after clinical studies of the highest standard have demonstrated safety and efficacy and regulatory approval pathways have been cleared, close attention must be paid to ensuring the safety and effectiveness of interventions that have entered routine or commercial clinical use, and the fairness of access in a manner consistent with local legal requirements and standards and the standards of ethical, evidence-based medicine. These standards include ongoing monitoring of safety and outcomes, and ensuring accessibility to those who have the most pressing clinical need.

Bio- and Pharmacovigilance

Recommendation 3.5.1.2: **Developers, manufacturers, providers, and regulators of stem cell-based interventions should continue to systematically collect and report data on safety, efficacy, and utility after they enter clinical use.**

Stem cell-based interventions can remain biologically active for long periods and thus may present risks with long latencies. Additionally, stem cells and their derivatives can exhibit a range of dynamic biological activities and therefore be potentially difficult to predict and control. These may lead to pathologies including tumorigenesis, hyperplasia, and the secretion of bioactive factors that may exert secondary effects on physiological processes such as inflammation or immune response. Some types of stem cells are capable of migration after transplantation, meaning there is a risk of off-target effects and inappropriate integration. Further, tracking the locations of transplanted cells may be difficult using current technologies.

For these reasons, monitoring patients' overall health status over the long term is critical, and plans for the funding and conduct of long-term monitoring should be incorporated into study protocols early in the development of new interventions. These monitoring activities may include systematic post-market studies, event and outcome reporting by providers and/or patients, patient registries, and/or economic analyses of comparative effectiveness. Results of such monitoring activities should be promptly reported to regulatory authorities and the medical community.

Patient Registries

Recommendation 3.5.1.3: **Registries of specific patient populations can provide valuable data on safety and outcomes of stem cell-based interventions within defined populations but should not substitute for stringent evaluation through clinical trials prior to introduction into standard care.**

Stakeholders in stem cell-based therapeutics, including researchers, physicians, regulatory bodies, industry, and patient and disease advocacy groups, should cooperate to develop safety and outcome registries to collect additional data on stem cell-based interventions that have been validated for clinical use.

Off-label Use

Recommendation 3.5.1.4: **Off-label uses of stem cell-based interventions should be employed with particular care, given uncertainties associated with stem cell-based interventions.**

Physicians may use interventions for indications or patient populations other than those for which they have been shown to be safe and effective. Such off-label applications constitute a common aspect of medical practice. Nevertheless, they present distinct challenges for stem cell-based interventions.

First, depending on the jurisdiction, some stem cell-based interventions are not authorized for a specific use due to exemption from regulation. This can limit physicians' access to reliable information on validated uses. Second, the complex biological properties of living cells and the limited clinical experience with cell-based therapies present uncertainties about long-term safety and effectiveness. Physicians should therefore exercise particular care when applying stem cell-based interventions off label. As a rule, off-label use should be offered only when supported by high quality evidence or in situations consistent with current scientific knowledge, local legal and institutional regulations, and the standards of the international medical community. Patients must be informed in advance if a proposed off-label use has not been evaluated for safety and/or efficacy with respect to their specific medical condition.

As a general principle, physicians should conduct controlled, supervised studies to establish safety and efficacy for new applications of products or interventions that have been approved in a distinct clinical setting.

3.5.2 ACCESS AND ECONOMICS

Support for stem cell research depends, in part, on its potential for advancing scientific knowledge, which may result in the development of clinical applications. As such, institutions, researchers, and providers in both the public and private sectors have a responsibility to promote public benefit, and specifically to ensure that research findings and benefits thereof are accessible to the international scientific community and, importantly, to those in need. The stem cell research community benefits from providing patients and the general public access to scientific information, opportunities to participate in clinical research, and treatment. For these reasons, research, clinical, and commercial activities should seek to maximize affordability and accessibility.

Comparative Value for Healthcare Systems and Access Issues

Recommendation 3.5.2.1: **Stem cell-based interventions should be developed with an eye towards delivering economic value to patients, payers, and healthcare systems.**

The development and provision of clinical interventions is based on decisions made by patients, healthcare professionals, and payers. Key factors that influence such decisions include the known risks and benefits of available treatment options, individual preferences on the part of patients and treatment providers, and comparative availability and cost. Developers, manufacturers and providers of stem cell-based interventions should recognize that, along with safety, efficacy and accessibility, economic value is an important measure of the overall utility of any therapeutic. They should thus participate in studies intended to assess comparative effectiveness, particularly in countries in which such studies are legally mandated. Such studies involve the systematic comparison of currently available therapies for their full range of benefits, and provide important information for medical decision-making.

Pricing

Recommendation 3.5.2.2: **Developers, funders, providers, and payers should work to ensure that cost of treatment does not prevent patients from accessing stem cell-based interventions for life-threatening or seriously debilitating medical conditions.**

Sponsors of research aimed at the development of stem cell-based interventions targeting seriously debilitating or life-threatening medical conditions should seek to support access to safe and efficacious therapeutics to any patient in need, irrespective of financial status. Access for individuals who participated in clinical research leading to the development of a licensed stem cell therapy is a particular priority.

Private firms seeking to develop and market stem cell-based interventions should work with public and philanthropic organizations to make safe and effective products available on an affordable basis to disadvantaged patient populations. Developers, manufacturers and patient groups should work engage with government regulators and health care funders to develop mechanisms for prompt and sustainable adoption of stem cell interventions for life-threatening or seriously debilitating medical conditions. Such mechanisms should balance the needs of those patients who will benefit with the responsibility of payers to the communities they serve, and strengthen the evidence base for the safety, effectiveness and long-term value of those therapies.

4. COMMUNICATIONS

Stem cell research receives a great deal of attention from policy makers, the popular press, and popular culture, including social media. Given its scientific and clinical potential and the controversies that have surrounded the field, this high public profile is understandable. However, popular coverage and reporting in the medical literature are frequently far from ideal. Potential benefits are sometimes exaggerated and the challenges to clinical application and risks are often understated. Inaccurate or incomplete representations of this sort can have tangible impacts on the expectations of the general public, patient communities, physicians, and on the setting of health and science policies. Inaccurate or incomplete representations can also be exploited by companies and individuals marketing stem cells for unproven clinical uses.

Public Representation of Science

Recommendation 4.1: **The stem cell research community should promote accurate, balanced, and responsive public representations of stem cell research.**

The high level of public and media interest in the field provides stem cell scientists with ample opportunities to communicate their findings through a variety of popular and social media. The research community is encouraged to engage interactively with the public through responsive outreach and communications and by providing opportunities for public comment and feedback.

While such opportunities may allow scientists to gain recognition and understanding for their work among non-specialists, they also have the potential to fuel inaccurate public perceptions about the current state of scientific progress, potential for application, and associated risks and uncertainties (Kamenova and Caulfield, 2015). Scientists, clinicians, science communications professionals at academic and research institutions, and industry spokespersons should strive to ensure that benefits, risks, and uncertainties of stem cell science are not misrepresented. Additionally, due to public interest and concern in the ethics of hESC research, and in order to ensure complete transparency of research and translational activities, the origin of stem cell materials should be clearly specified in all communications.

Care should be exercised throughout the science communication process, including in the presentation of results, the promotion of research and translation activities, the use of social media, and any communication with print and broadcast media. Researchers should make efforts to seek timely corrections of inaccurate or misleading public representations of research projects, achievements, or goals. Scientists should also be particularly careful about disclosing research findings that have not passed peer review, as premature reporting can undermine public confidence if findings are subsequently disproven. Likewise, forward-looking statements on inherently uncertain developments, such as predictions on time required until clinical application, the likelihood of product approval, or speculation on the potential economic impact of currently unrealized technologies, must be accurate, circumspect and restrained.

Scientists should work closely with communications professionals at their institution to create information resources that are easy to understand without oversimplifying, and that do not underplay risks and uncertainties. Similarly, research-sponsoring institutions and communications specialists, including journalists, have a responsibility to ensure that any informational materials referring to research achievements adhere to these principles, and that the scientists in charge of correspondence relating to the findings have reviewed and agreed to the content prior to release. For potentially sensitive or high-profile cases, it is advisable to seek additional comments from independent experts to ensure objectivity and balance.

Communications about Clinical Trials

Recommendation 4.2: **When describing clinical trials in the media or in medical communications, investigators, sponsors, and institutions should provide balance and not emphasize statistically significant secondary results when pre-specified primary efficacy results are not statistically significant. They should also emphasize that research is primarily aimed at generating systematic knowledge on safety and efficacy not therapeutic care.**

Too often, studies reporting statistically non-significant primary outcomes are "spun" by appealing to other findings, such as statistically significant secondary outcomes (Boutron et al., 2010). Such reporting practices can distort medical and public interpretation of trial results. When communicating results of clinical research, scientists, institutions, and journalists should clearly state the pre-specified primary endpoint of the study and whether or not it was reached with statistical significance.

Clinical trials designed to evaluate safety and/or efficacy should not be described using language that might suggest the primary intent to be the delivery of care, as this may lead to confusion about the risk/benefit profile of study participation (see also Recommendation 3.3.3.1). Communications about ongoing studies should explain that clinical efficacy is not established, and that the results may reveal the intervention to be ineffective or, in some cases, harmful.

Scientists engaged in clinical research should establish communications with relevant patient and advocacy groups to promote clear understanding of the clinical research process and the current state of progress in developing stem cell-based treatments for specific medical conditions. Accordingly, all involved in clinical research, including not only investigators and sponsoring institutions but also patients, families and advocacy groups, should exercise caution when communicating with the public. Additionally, researchers should exercise great care when making forward-looking statements regarding the potential outcome of any study.

Communications about Clinical Care

Recommendation 4.3: **The provision of information to patients on stem cell-based interventions must be consistent with the primacy of patient welfare and scientific integrity.**

The provision of accurate information on risks, limitations, possible benefit, and available alternatives to patients is essential in the delivery of healthcare. Provision of clinical information, including recommendations on use, should center on the importance of consultation with medical professionals directly familiar with the individual patient's case, and the seeking of independent expert opinion. The goal of clinical communications is to enable autonomous, well-informed decision-making by patients.

Given the novelty of stem cell-based interventions and the fact that many countries do not have well-established regulatory pathways governing the introduction of novel medical products into clinical use, providers should exercise restraint in their communications regarding the clinical utility of such treatments. The use of language that could be construed as promotional, promissory, or suggestive of clinical effectiveness in reference to stem cell-based interventions for which efficacy has not been established is to be avoided. In the event that new stem cell-based interventions are authorized for use for a specified indication, care must be taken to avoid communications that might indicate or suggest to patients that such intervention is efficacious for other indications.

Regulatory and law enforcement authorities are encouraged to investigate and, when appropriate, restrict unsupported marketing claims made by commercial actors, to the extent that these violate relevant consumer protection, truth in advertising, securities, and commerce laws within a given jurisdiction.

5. STANDARDS IN STEM CELL RESEARCH

Translation of cell-based interventions is a collaborative endeavor among scientists, clinics, industry, regulators, and patients. Standards help enable such collaborations, and support efficient clinical translation in many ways. For instance, they allow scientists to compare outcomes of trials and enable clinics to reproduce treatments reported in published studies. Regulatory standards also reduce the costs of uncertainty for private actors, facilitate independent review, and engender trust among patients.

Standards Development

Recommendation 5.1: **Researchers, industry and regulators should work towards developing and implementing standards on design, conduct, interpretation, and reporting of research in stem cell science and medicine.**

There are numerous areas where standards development would greatly advance the science of stem cells and its clinical application. Particular opportunities include standards for: (a) consent and procurement, (b) manufacturing regulations, (c) cell potency assays, (d) reference materials for calibrating instruments, (e) minimally acceptable changes during cell culture, (f) method of delivery and selection of recipients for novel stem cell-based interventions, (g) reporting of animal experiments, (h) design of trials, (i) reporting of trials, (j) principles for defining information in datasets as "sensitive" such that there is a justified withholding or delay of study reporting.

The ISSCR encourages scientists, regulators, funders, and others involved in stem cell research to collaborate on timely development of standards for stem cell research and translation. To promote common and universal standards for consent and procurement of biomaterials, the ISSCR has provided template donor consent forms (Appendix 2).

Revisiting Ethical Guidelines

Recommendation 5.2: **These guidelines should be periodically revised to accommodate scientific advances, new challenges, and evolving social priorities.**

New medical opportunities and ethical challenges in the conduct of stem cell research and assisted reproductive technologies that are on the horizon must be addressed in a timely manner to ensure that science and medical care proceeds in a socially responsible and ethically acceptable fashion. Periodic revision enhances 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.

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APPENDICES

Appendix 1.

INFORMED CONSENT CONSIDERATIONS FOR PROCUREMENT OF BIOMATERIALS FOR STEM CELL RESEARCH AND TRANSLATION

The informed consent process for the procurement of biomaterials procurement for stem cell research and translation should cover the following statements, adapted to the particular project:

a. That the biomaterials will be used in the derivation of totipotent or pluripotent cells for research.

b. That the biomaterials will be destroyed during the process of deriving totipotent or pluripotent cells for research.

c. That derived cells and/or cell lines might be deposited and stored in a repository many years and used internationally for future studies, many of which may not be anticipated at this time.

d. That cells and/or cell lines might be used in research involving genetic manipulation of the cells, the generation of human-animal chimeras (resulting from the transfer of human stem cells or their derivatives into animal models), or the introduction of stem cells or their derivatives into human or animal embryos.

e. 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 or directed altruistic donation.

f. Whether the donation is limited to specific research purposes or is for broadly stated purposes, including research and/or clinical application 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 a human subjects review committee. The consent process should explore and document whether donors have objections to the specific forms of research and/or clinical application outlined in the research protocol.

g. Whether the donor may be approached in the future to seek additional consent for new uses or to request additional materials (such as blood or other clinical samples) or information.

h. Disclosure of what donor medical or other information and what 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.

i. 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.

j. Disclosure of any present or potential future financial benefits to the investigator and the institution related to or arising from proposed research.

k. 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 the community.

l. That neither consenting nor refusing to donate biomaterials for research will affect the quality of care provided to potential donors.

m. That there are alternatives to donating human biomaterials for research, and an explanation of what these alternatives are.

n. For donation or creation of embryos, that the embryos will not be used to attempt to produce a pregnancy and will not be allowed to develop in culture in vitro for longer than 14 days from fertilization.

o. 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.

p. That nucleic acid sequencing of the resulting stem cell line is likely to be performed and this data may be stored in databases available to the public or to qualified researchers with confidentiality provisions, and that this may compromise the capacity for donation to remain anonymous and/or de-identified.

q. That the donor and/or biomaterials will be screened for infectious and possibly genetic diseases or markers of disease.

r. Whether there is a plan to share with the biomaterials donor any clinically relevant health information discovered incidentally during the course of research.

Appendix 2.
SAMPLE INFORMED CONSENT DOCUMENTS FOR PROCUREMENT OF HUMAN BIOMATERIALS FOR STEM CELL RESEARCH

A2.1 EMBRYO DONATION FOR STEM CELL RESEARCH: CREATED FOR FERTILITY PURPOSES AND IN EXCESS OF CLINICAL NEED

http://www.isscr.org/docs/default-source/guidelines/CFembryos.doc

A2.2 SOMATIC CELL DONATION FOR INDUCED PLURIPOTENT STEM CELL RESEARCH

http://www.isscr.org/docs/default-source/guidelines/CFsomaticcells.doc

A2.3 EGG DONATION FOR STEM CELL RESEARCH; PROVIDED DIRECTLY AND SOLELY FOR STEM CELL RESEARCH

http://www.isscr.org/docs/default-source/guidelines/CFeggsforresearch.doc

A2.4 EGG DONATION FOR STEM CELL RESEARCH; COLLECTED DURING THE COURSE OF FERTILITY TREATMENT AND IN EXCESS OF CLINICAL NEED

http://www.isscr.org/docs/default-source/guidelines/CFeggsexcessofclinical.doc

A2.5 SPERM DONATION FOR STEM CELL RESEARCH

http://www.isscr.org/docs/default-source/guidelines/CFsperm.doc

Appendix 3.
SAMPLE MATERIAL TRANSFER AGREEMENT DOCUMENT

A3.1 SAMPLE MATERIAL TRANSFER AGREEMENT (MTA)

http://www.isscr.org/docs/default-source/guidelines/MTA.doc

GLOSSARY

Definitions and discussion of terminology relevant to these guidelines. Other definitions can be found at http://stemcells.nih.gov.

G.1 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. 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 preimplantation 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 (for example, 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 two 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 20-35 hours after insemination with sperm.

Cleavage stage embryo (preimplantation stage): The embryonic stage that follows the first division of the zygote and ends upon morula compaction; precise stages include the two-cell, four-cell, eight-cell and 16-cell embryo. In humans, each cleavage division takes around 18-24 hours.

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

Blastocyst: The embryonic stage formed starting around 64 cells, defined by the pumping of fluid into an internal space that becomes the blastocoel cavity. The outer cell layer of the blastocyst is a ring of differentiated trophectoderm cells, which encloses a nest of 10-25 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 five-seven days after fertilization. The blastocyst hatches from the zona pellucida (a surrounding glycoprotein shell) around days six-seven after fertilization. Thereafter, and coupled to implantation, the ICM of the blastocyst begins to organize itself into a long axis with anterior and posterior orientation.

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 in non-human animals, parthenogenetic embryos have been observed to progress to a fetal stage but further development is compromised by an underdeveloped placental system that prevents normal gestation. Gynogenesis is a particular form of parthenogenesis in which an embryo is created from the genetic contributions (female pronuclei) of two different fertilized oocytes. Androgenesis entails creation of an embryo that incorporates the male pronuclei from two different fertilized oocytes.

Embryo-like structures: Advances in cellular engineering make possible the assembly, differentiation, aggregation, or re-association of cell populations in a manner that mimics or recapitulates key stages of embryonic development. Such experimental systems can provide essential insights into tissue and organ development but raise concerns when such structures achieve complexity through engineering or self-organization to the point where they might realistically manifest human organismal form or developmental potential. Because the restrictions on preimplantation embryo culture beyond 14 days or formation of the primitive streak were not written to apply to embryo-like structures, the guidelines specify the imperative for specialized review when experimentally generated embryo-like structures might manifest human organismal form, integrated organ system development, autonomous developmental capacity, or full organismal potential as defined by expert review. A guiding principle of review should be that embryo-like structures that might manifest human organismal form or developmental potential be maintained in culture for no longer than the minimal time needed to address a scientific question deemed highly meritorious by a rigorous review process.

Nuclear Transfer: involves 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.

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.

G.2 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.

Multipotent: The state of single cells that are capable of differentiating into multiple cell types, but not all of the cells of an organism. Multipotent cells, exemplified by the hematopoietic stem cell, give rise to a range of cells within a specific tissue. Within the developing organism multipotent cells may give rise to derivatives of more than one embryonic germ layer, as for mesendodermal progenitors. In the adult, multipotent cells are typically restricted to becoming derivatives

of a specific germ layer (endoderm, ectoderm, mesoderm).

Unipotent: The state of single cells that are capable of differentiating only along a specific cell lineage, and are exemplified by lineage-committed progenitors of the hematopoietic system (for example, erythroblasts). Unipotent stem cells undergo self-renewal and differentiation along a single lineage, as exemplified by the spermatogonial stem cell.

Teratoma: a benign, encapsulated mass of complex differentiated tissues comprising elements of all three embryonic germ layers: ectoderm, endoderm, and mesoderm. In the context of stem cell research, the teratoma assay entails injection of cell populations into immune-deficient murine hosts to assess their pluripotency (their capacity to form all tissues in the body).

G.3 THE TERM "CHIMERA" IN STEM CELL RESEARCH

Chimera: an organism carrying cell populations derived from two or more different zygotes of the same or different species.

Trace chimeras: The simplest form of chimera is one in which a limited number of human cells are introduced to another organism 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 immunodeficient 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: (a) those formed at the earliest stages of development if there is capacity for widespread chimerism, and (b) those formed later but contributing a significant degree of chimerism to the central nervous system and/or germline. Human-to-non-human primate chimeras formed at any stage of development warrant particular attention. Human-to-non-human chimeras bearing central nervous system chimerism also warrant particular attention. For additional guidance on the review of human-animal chimeras, please consult the white paper from the ISSCR Ethics and Public Policy Committee (Hyun et al., 2007).

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).

G.4 TERMS USED IN TRANSPLANTATION

Allogeneic transplantation: refers to the transplantation of cells from a donor to another person, either related (as when from a sibling or parent) or from an unrelated individual. In hematopoietic stem cell transplantation, unrelated donors may be identified from large donor registries as being histocompatible, or matched to the transplant recipient at a series of human leukocyte antigens known to mediate transplant rejection. Allogeneic hematopoietic stem cell transplantation carries with it the potential for the donor's transplanted cells to mount an immune attack against the recipient (graft versus host disease), while solid organ transplant carries the risk of the recipient's immune system rejecting the allograft. Both clinical settings require the use of immunosuppressive drugs, which in the case of solid organ transplant recipients must be taken lifelong, placing them at risk of infectious complications.

Autologous transplantation: refers to the transplantation to a patient of his/her own cells. Because the cells are recognized by the patient's immune system as "self," no rejection or immune-incompatibility is observed. Consequently, autologous transplantation of cells typically carries fewer risks than allogeneic transplantation. Generation of embryonic stem cells by somatic cell nuclear transfer or derivation of induced pluripotent stem cells by reprogramming offers a source of autologous cells for transplantation studies which offer the theoretical advantage of immune compatibility.

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, or the use of mesenchymal stem cells to repair bone or cartilage.

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

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

G.5. TERMS PERTAINING TO RESEARCH SUBJECTS AND CLINICAL RESEARCH

Clinical research: any systematic research conducted

with human subjects or groups of human subjects or on materials from humans, such as tissue samples.

Clinical trials: any research study that prospectively assigns human subjects or groups of human subjects to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, diagnostics, devices, behavioral treatments, process-of-care changes, preventive care.

Correlative studies: Studies, typically occurring within clinical trials, that explore the cause and effects of an intervention on biological targets involved in a disease process or linkages among groups or different elements of a group.

Observational studies: a type of clinical research where investigators observe human subjects or groups of human subjects to measure variables of interest; the assignment of subjects into a treated group versus a control group is not controlled by the investigator.

Sham procedures: procedures used as controls in clinical trials that mimic experimental procedures for research subjects in the "treatment" arm. These are performed to prevent research subjects and physicians assessing their outcomes from knowing which arm of the trial the subject has been enrolled in. They are also sometimes performed to control for the effects treatment delivery (rather than the treatment per se) has on a disease process. Sham procedures vary in their invasiveness. Examples include saline injections (where research subjects are injected with saline instead of cells), sham cardiac catheterization (where research subjects receive cardiac catheterization but are not injected with cells), and partial burr holes to the cranium (where researchers imitate the experience of receiving brain surgery by drilling a depression in the skull).

Minimal risk: risk from procedures to human subjects or tissue donors that is comparable to the probability and the magnitude of harms that are ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Minor increase over minimal risk: an increment in risk that is only a fraction above the minimal risk threshold and considered acceptable by a reasonable person.

Incidental finding: a discovery concerning an individual research participant or tissue donor that does not relate directly to the aims of a study but that has potential health or reproductive importance for the individual.

Assent: in the context of clinical research, assent means the participant agrees to take part. To give assent means that the participant is engaged in research decision-making in accordance with his or her capacities. Children and adolescents who are legal minors cannot give legally valid informed consent but they may be able to give assent. Assent demands that the legal minor provide affirmative agreement to participate in research.

Compensation: payment for research subjects' non-financial burdens incurred during the course of their research participation, most commonly their time, effort, and inconvenience.

Reimbursement: repayment for research subjects' out-of-pocket expenses incurred during their participation in research.

Undue inducement: an offer or reward so attractive that it threatens to impair the ability of prospective research subjects or donors to exercise proper judgment, or it encourages them to agree to procedures for which they are strongly averse.

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