

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Daley, GQ;Hyun, I;Apperley, JF;Barker, RA;Benvenisty, N;Bredenoord, AL;Breuer, CK;Caulfield, T;Cedars, MI;Frey-Vasconcells, J;Heslop, HE;Jin, Y;Lee, RT;McCabe, C;Munsie, M;Murry, CE;Piantadosi, S;Rao, M;Rooke, HM;Sipp, D;Studer, L;Sugarman, J;Takahashi, M;Zimmerman, M;Kimmelman, J

Title:

Setting global standards for stem cell research and clinical translation: The 2016 ISSCR guidelines

Date:

2016-06-14

Citation:

Daley, G. Q., Hyun, I., Apperley, J. F., Barker, R. A., Benvenisty, N., Bredenoord, A. L., Breuer, C. K., Caulfield, T., Cedars, M. I., Frey-Vasconcells, J., Heslop, H. E., Jin, Y., Lee, R. T., McCabe, C., Munsie, M., Murry, C. E., Piantadosi, S., Rao, M., Rooke, H. M. ,... Kimmelman, J. (2016). Setting global standards for stem cell research and clinical translation: The 2016 ISSCR guidelines. Stem Cell Reports, 6 (6), pp.787-797. <https://doi.org/10.1016/j.stemcr.2016.05.001>.

Persistent Link:

<https://hdl.handle.net/11343/262348>

License:

CC BY-NC-ND

Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines

George Q. Daley,^{1,*} Insoo Hyun,² Jane F. Apperley,³ Roger A. Barker,⁴ Nissim Benvenisty,⁵ Annelien L. Bredenoord,⁶ Christopher K. Breuer,⁷ Timothy Caulfield,⁸ Marcelle I. Cedars,⁹ Joyce Frey-Vasconcells,¹⁰ Helen E. Heslop,¹¹ Ying Jin,¹² Richard T. Lee,¹³ Christopher McCabe,¹⁴ Megan Munsie,¹⁵ Charles E. Murry,¹⁶ Steven Piantadosi,¹⁷ Mahendra Rao,^{18,19} Heather M. Rooke,²⁰ Douglas Sipp,^{21,22} Lorenz Studer,²³ Jeremy Sugarman,²⁴ Masayo Takahashi,²⁵ Mark Zimmerman,²⁶ and Jonathan Kimmelman^{27,*}

¹Division of Hematology/Oncology, Boston Children's Hospital and Dana Farber Cancer Institute, Boston, MA 02115, USA

²Department of Bioethics, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA

³Centre for Hematology, Imperial College, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

⁴John van Geest Centre for Brain Repair, Department of Clinical Neuroscience, Cambridge CB2 0PY, UK

⁵Department of Genetics, The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

⁶Department of Medical Humanities, Julius Center, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands

⁷Center for Cardiovascular Research, Nationwide Children's Hospital, Columbus, OH 43215, USA

⁸Health Law Institute, University of Alberta, Edmonton, AB T6G 2H5, Canada

⁹University of California San Francisco School of Medicine, San Francisco, CA 94158, USA

¹⁰Frey-Vasconcells Consulting, Sykesville, MD 21784, USA

¹¹Center for Cell & Gene Therapy, Baylor College of Medicine, Houston Methodist Hospital and Texas Children's Hospital, Houston, TX 77030, USA

¹²Institute of Health Science, Shanghai JiaoTong University School of Medicine/Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Shanghai, 200025, China

¹³Harvard Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge MA 02138, USA

¹⁴Department of Emergency Medicine, University of Alberta, Edmonton, AB T6G 2B7, Canada

¹⁵Education, Ethics, Law & Community Awareness Unit, Stem Cells Australia, Department of Anatomy and Neuroscience, University of Melbourne, Melbourne, Parkville, VIC 3010, Australia

¹⁶Departments of Pathology, Bioengineering and Medicine/Cardiology, Institute for Stem Cell and Regenerative Medicine, Center for Cardiovascular Biology, University of Washington, Seattle, WA 98109, USA

¹⁷Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

¹⁸The New York Stem Cell Foundation Research Institute, New York, NY 10023, USA

¹⁹Q Therapeutics, Salt Lake City, UT 84108, USA

²⁰International Society for Stem Cell Research, Skokie, IL 60077, USA

²¹RIKEN Center for Developmental Biology, Kobe, 650-0047 Japan

²²Keio University School of Medicine, Tokyo, 160-8582 Japan

²³Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

²⁴Johns Hopkins Berman Institute of Bioethics, Baltimore, MD 21205, USA

²⁵Center for Developmental Biology, RIKEN, Kobe, Hyogo 650-0047, Japan

²⁶ViaCyte, San Diego, CA 92121, USA

²⁷Biomedical Ethics Unit, McGill University, Montreal, QC H3A 1X1, Canada

*Correspondence: george.daley@childrens.harvard.edu (G.Q.D.), jonathan.kimmelman@mcgill.ca (J.K.)
<http://dx.doi.org/10.1016/j.stemcr.2016.05.001>

The International Society for Stem Cell Research (ISSCR) presents its 2016 Guidelines for Stem Cell Research and Clinical Translation (ISSCR, 2016). The 2016 guidelines reflect the revision and extension of two past sets of guidelines (ISSCR, 2006; ISSCR, 2008) to address new and emerging areas of stem cell discovery and application and evolving ethical, social, and policy challenges. These guidelines provide an integrated set of principles and best practices to drive progress in basic, translational, and clinical research. The guidelines demand rigor, oversight, and transparency in all aspects of practice, providing confidence to practitioners and public alike that stem cell science can proceed efficiently and remain responsive to public and patient interests. Here, we highlight key elements and recommendations in the guidelines and summarize the recommendations and deliberations behind them.

As the largest international professional organization engaged with stem cell research, the International Society for Stem Cell Research (ISSCR) has promoted both rigorous scientific inquiry and careful ethical deliberations regarding stem cell science and regenerative medicine. Through its Guidelines for the Conduct of Human Embryonic Stem Cell Research (ISSCR, 2006) and Guidelines for the Clinical Translation of Stem Cells (ISSCR, 2008), the ISSCR has set high standards, offering concrete mechanisms for review and conduct of research and clinical develop-

ment. These guidelines were designed to promote rapid yet responsible advances in fundamental knowledge and the clinical application of stem cell science. However, in the decade since the release of the first ISSCR guidelines, stem cell science has made remarkable advances but has also encountered numerous new ethical, social, and policy challenges. For example, new discoveries and techniques such as gene editing or mitochondrial replacement offer bold possibilities while also posing ethical conundrums. Moreover, stem cell science and clinical application are increasingly



pursued across geographical and boundaries, necessitating the need for policies that can be applied internationally. In an effort to keep pace with these many new developments and future prospects, the ISSCR has undertaken a comprehensive revision of its guidelines to account for scientific progress, policy developments, globalization of stem cell activities, and evolving ethics scholarship.

Below, we highlight what has been preserved and what is new in the 2016 ISSCR Guidelines for Stem Cell Research and Clinical Translation. We also provide a window into our deliberations and describe key elements of the process from which these revised guidelines emerged. Specific recommendations embodied in the document are presented in [Table 1](#), giving the reader a synopsis of core principles.

Core Tenets Preserved

The revised guidelines reassert many of the bedrock tenets of the ISSCR's 2006 and 2008 guidelines. At their core, the 2016 guidelines preserve the general imperative that ethically sensitive stem cell research projects should undergo a specialized oversight process. This oversight process, which earlier ISSCR guidelines labeled Stem Cell Research Oversight (SCRO), enlists stem cell-specific expertise and ethical review that acknowledge the uniquely sensitive aspects of research involving human embryos. The 2016 guidelines retain the original three categories of research that guide the oversight process. Category 1 allows routine aspects of research to be conducted under a streamlined process of administrative approval (for example, work with existing human embryonic stem cell or hESC lines). Category 2 defines research projects warranting special scrutiny (for example, derivation of new hESC lines). Category 3 describes impermissible research (for example, reproductive cloning and extended in vitro culture of human embryos beyond 14 days or formation of the primitive streak). Also retained is the requirement for review of certain human-animal chimera experiments, when high degrees of central nervous system or germ lineage chimerism are anticipated. The requirement for explicit consent from donors is emphasized for use of their biomaterials in sensitive aspects of stem cell research, such as the derivation of new hESC lines, generation of embryos via somatic cell nuclear transfer, or future use in commercial development. To facilitate widespread adoption of the informed consent principles embodied in these guidelines, the ISSCR is providing template informed consent documents that can be downloaded and customized to specific protocols (<http://www.isscr.org>). In the realm of clinical translation, the 2016 guidelines retain stringent standards of preclinical evidence and high aspirations for understanding the mechanism of action of stem cell-based interventions prior to clinical trials. The updated guidelines restate a strong condemnation of the now widespread marketing and de-

livery of unproven stem cell-based interventions, practices that free-ride on the excitement of stem cell science but have little scientific basis and exploit the hopes of patients and their families.

New Format, Principles, and Formulations

The 2016 guidelines break new ground in several areas. They encompass a broader and more expansive scope of research and clinical endeavor and speak assertively to contentious issues of regulatory practice, the cost of regenerative medicine products, and public communication. The 2016 guidelines are now presented as a single document, with a preamble that articulates core ethical principles for guiding both basic and clinical stem cell research: the integrity of the research enterprise, the primacy of patient welfare, respect for research subjects, transparency, and social justice. These principles provide a foundation for the recommendations that follow in the guidelines and inform their interpretation.

Among the most significant changes is the scope of research that warrants specialized review. Given that human induced pluripotent stem cells (iPSCs) do not engender the same sensitivities as derivation of new hESC lines, the new guidelines exclude the derivation of iPSCs from specialized review, instead calling upon committees that oversee human subjects to scrutinize donor cell procurement. Protocols that employ human iPSCs to achieve human-animal chimerism of the central nervous system or the admixture of human iPSCs with human embryos will, however, still trigger specialized review.

Acknowledging that stem cell researchers engage in many forms of human embryo research that do not explicitly involve derivation or use of hESC lines, the guidelines broaden the scope of specialized review beyond the SCRO function to encompass all forms of human embryo research. The 2016 guidelines specify a process of embryo research oversight (EMRO), which encompasses both embryonic stem cell research and any human embryo research that may not explicitly pertain to stem cells or stem cell lines, such as single cell analyses, genome modification, and embryo chimerism. At present, the guidelines for EMRO review represent the most comprehensive set of principles to inform oversight of the emerging technologies being applied to human embryo research and are consistent with embryo research policy statements by the [American College of Obstetricians and Gynecologists \(2006\)](#), the [American Society for Reproductive Medicine \(Ethics Committee of American Society for Reproductive Medicine, 2013\)](#), the [European Society for Human Reproduction and Reproductive Endocrinology \(ESHRE Taskforce on Ethics and Law, 2001\)](#), and the [Human Fertilisation and Embryology Authority \(HFEA\) of the United Kingdom](#).



Table 1. Summary of Recommendations from the ISSCR Guidelines for Stem Cell Research and Clinical Translation

Section	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.
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.
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.
2.1.4	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.
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 germline 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.
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.
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.
2.2.3	Review of procurement protocols must ensure that biomaterials donors are adequately informed about the specific aspects of their voluntary research participation.
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.
2.2.5	For provision of oocytes for research, when oocytes are collected outside the course of clinical treatment, compensation for nonfinancial burdens should not constitute an undue inducement.
2.2.6	Informed consent for research donation must be kept distinct from informed consent for clinical treatment.
2.2.7	The informed consent process and study design of human biomaterials procurement should be robust.
2.3.1	Proposals for derivations of new human embryonic stem cell 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.
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.
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.
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.

(Continued on next page)



Table 1. *Continued*

Section	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.
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.
2.4.1	These ISSCR guidelines should be upheld and enforced through standards of academic, professional, and institutional self-regulation.
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.
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.
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, good manufacturing practice (GMP) should be followed.
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.
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.
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.
3.1.2.5	Funding bodies, industry, and regulators should work to establish a public database of clinically useful lines that contains adequate information to determine the lines' utility for a particular disease therapy.
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 nonanimal experimental platforms whenever possible.
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.
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.
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.
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.
3.2.2.3	For all cell-based products, whether injected locally or systemically, researchers should perform detailed and sensitive biodistribution studies of cells.
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.
3.2.2.5	Preclinical researchers should adopt practices to address long-term risks and to detect new and unforeseen safety issues.
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.

(Continued on next page)



Table 1. *Continued*

Section	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 very strong evidence of efficacy using similar products against similar human diseases.
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.
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.
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.
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.
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.
3.3.2.1	Launch of clinical trials should be supported by a systematic appraisal of evidence supporting the intervention.
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.
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.
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.
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.
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.
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.
3.3.2.8	Research teams must protect the privacy of human subjects.
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.
3.3.3.1	Consent procedures in any preclosure phase, but especially early phase trials of stem cell-based interventions, should work to dispel potential research subjects' overestimation of benefit and therapeutic misconception.
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.
3.3.3.3	Researchers should take measures to maximize the scientific value of early phase trials.
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.

(Continued on next page)



Table 1. *Continued*

Section	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.
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.
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.
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.
3.3.6.1	All trials should be prospectively registered in public databases.
3.3.6.2	Investigators should report adverse events including their severity and their potential causal relationship with the experimental intervention.
3.3.6.3	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.
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.
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.
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.
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.
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.
3.5.2.1	Stem cell-based interventions should be developed with an eye toward delivering economic value to patients, payers, and healthcare systems.
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.
4.1	The stem cell research community should promote accurate, balanced, and responsive public representations of stem cell research.
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.
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.
5.1	Researchers, industry, and regulators should work toward developing and implementing standards on design, conduct, interpretation, and reporting of research in stem cell science and medicine.
5.2	These guidelines should be periodically revised to accommodate scientific advances, new challenges, and evolving social priorities.



In concordance with recent deliberations in the United Kingdom, the United States, and elsewhere, the 2016 guidelines articulate principles for evaluating both basic and clinically applied research on mitochondrial replacement in embryos aimed at preventing transmission of diseases that are caused by mutations in the mitochondrial genome. In addition, the 2016 guidelines consider basic research on editing of the nuclear genomes of embryos in the permissible category, subject to a rigorous EMRO process. However, given current uncertainties about the safety of nuclear genome editing and a lack of societal consensus on whether any form of heritable nuclear genome editing should be allowed, the guidelines consider uterine transfer of human embryos that have undergone modification of their nuclear genome impermissible at this time. Nonetheless, we recognize that the potential benefits and harms of such technologies remain poorly understood and that more scientific research and ethical inquiry are needed to inform future policy.

Another aspect of the guidelines that has evolved over time is the permissibility of compensating women who provide oocytes for research. Based on a white paper from the ISSCR Ethics and Public Policy Committee ([Haimes et al., 2013](#)), the new recommendations reflect an evolving consensus that compensating women who provide oocytes can be ethically permissible. The 2016 guidelines specify a review to determine appropriate compensation for oocyte providers' nonfinancial burdens, so long as such payments do not constitute an undue financial inducement to participate.

Researchers are developing novel methods to probe human development, including the formation of complex organoids and embryo-like structures that manifest potential for self-organization. Experiments wherein tissue aggregates manifest markers of the human primitive streak (for example, [Warmflash et al., 2014](#)) or in which human embryos are cultured to reveal post-implantation stages of development (for example, [Deglincerti et al., 2016](#) and [Shahbazi et al., 2016](#)) challenge the time-honored limitations of human embryo culture, widely known as the "14 day rule." Embodied in the 1984 Warnock commission report issued in the wake of the first practice of in vitro fertilization ([Warnock, 1985](#)), the 14 day rule precludes culture of intact preimplantation human embryos beyond the point of streak formation or 14 days. Applying the standard of primitive streak formation requires judgment and in light of advances in organoid biology, synthetic biology, chimera research, tissue engineering, and recent experiments that have extended embryo culture, there have been recent calls for its reassessment ([Hyun et al., 2016](#)). Still more challenging, the task force has provided principles of review for experiments in which human cells might self-organize into embryo-like structures

with the realistic potential to become a living organism. The task force concluded that human embryo-like structures at any stage of development should not be maintained in culture for more than the minimal period of time necessary for the study, with the scientific merit of the experiments evaluated in a rigorous EMRO process. Here again, the ISSCR guidelines articulate a core principle to be interpreted by local review, subject to local customs, mores, and legal restrictions. For this emerging area of research on human development, specific elements of review and the distinctions between permissible and impermissible experiments must be re-evaluated over time in light of scientific advances and continued deliberations.

New Stipulations for Preclinical Research, Clinical Translation, and Practice

Despite the relatively immature state of our scientific understanding of mechanisms of stem cell differentiation, transplantation, and tissue integration, clinical testing of stem cell applications has proceeded rapidly, and as judged by the task force, prematurely in many cases. Against calls for relaxed standards for autologous use of cell products, the guidelines retain an emphasis on high standards of cell processing and manufacture. Recent revelations that fungal contamination of drugs prepared by a United States pharmacy caused infections and dozens of deaths ([Smith et al., 2013](#)) serve as a reminder that injection into patients of any material, whether chemical or cellular, irrespective of the degree of ex vivo processing, carries the risk of devastating complications. The 2016 guidelines retain the high standard of good manufacturing practice (GMP) in the preparation of cell-based therapeutics.

The guidelines recognize the many opportunities for improving the conduct and reporting of preclinical studies in stem cell research. They recommend that human studies proceed only after rigorous demonstration of safety and efficacy in adequately powered preclinical studies and that clinical trial protocols be subject to rigorous peer review that scrutinizes the weight of preclinical evidence, and balances risk with opportunity, as appropriate to the stage of the trial. The guidelines have sought further to address the problem of irreproducibility of research, articulating high standards for preclinical design, study reporting, and an imperative to publish negative as well as positive results.

Guidance is provided regarding clinical trials involving subjects with diminished capacity. The guidelines also address the use of placebo and sham surgical controls, which have been criticized in the past in the context of studies of surgically implanted cell transplants for Parkinson's disease ([Macklin, 1999](#)). Patient funding of clinical trials and direct payments by patients to participate in clinical trials is a trend that, while making some research



possible, also raises concerns for the integrity of the research enterprise, objectivity, and patient welfare. The 2016 guidelines articulate a highly limited set of circumstances under which patients may provide funding for trials in which they enroll. New recommendations stipulate that protocols that involve patient funding undergo independent review for scientific rationale, priority, and design and be conducted with independent oversight.

New sections in the 2016 guidelines articulate high standards for transparency in the conduct and reporting of clinical trials, prospective registration in public databases (for example, <https://clinicaltrials.gov>), reporting of adverse events, and an imperative to publish both negative and equivocal results. Guidelines for the provision of innovative care outside of formal clinical trials have been strengthened and extended, as have admonitions against off-label use of approved cell-based therapies, given the uncertainties associated with heterologous applications of stem cells. A commentary devoted to aspects of clinical translation in the new guidelines appears elsewhere (Kimmelman et al., 2016a).

Social Justice

The 2016 guidelines encourage developers of stem cell-based medicines to aspire to social justice and fairness in their pricing of new products, stipulating that new therapies should provide economic value to patients, payers, and health care systems and that costs should not prevent patients from accessing stem cell interventions for life-threatening or seriously debilitating medical conditions. Developers are encouraged to engage in studies intended to assess comparative effectiveness, as legally mandated in some countries.

With rising commercial interest in stem cell-based medicines, some countries have adopted or are considering streamlined regulatory pathways that grant conditional marketing approval for regenerative medicine products after early stage trials that establish only a baseline of safety and some promise of efficacy. The task force vigorously debated the advantages and potential risks of regulatory changes in the standards of safety and efficacy required for marketed products. The deliberations of the task force and the recommendations embodied in the guidelines emphasize considerations of patient welfare and concerns for patient safety, equity, and the financial sustainability of health care systems. Fewer than one in ten drugs that enter early phase clinical testing gain regulatory approval, while roughly two-thirds of drugs that progress from phase I to more advanced stages ultimately fail for reasons of either safety or ineffectiveness (Waring et al., 2015). Striking the right balance between facilitating patient access to new therapies and rigorous evaluation of new therapies continues to present a challenge for drug regulation. Unless thoughtful

choices are made regarding which products are afforded expedited review and conditional marketing approval, regenerative medicine products approved based on early stage trial results could prove either unsafe or ineffective when tested more widely and rigorously. Noting examples where interventions entered clinical practice based on promising pilot clinical data that were ultimately not substantiated in randomized clinical trials (for example, high-dose chemotherapy and autologous bone marrow transplantation for advanced breast cancer; Rettig, 2007), the task force was wary that premature market authorization and clinical practice of unproven intervention strategies can slow their rigorous evaluation in formal trials and erode confidence in the scientific standards of the field. Moreover, there is concern that asking patients, insurance providers, and health care systems to bear the cost of therapies that might not be safe or effective would further stress health care systems and patients already burdened by rising costs.

A Call for Responsible Communication

The guidelines task force took special note of the rising visibility of stem cell research and the exuberance for clinical translation over the past decade. The new guidelines strengthen calls for responsible communication by scientists, clinicians, science communications professionals, industry spokespersons, and members of the media. Exaggeration of potential benefits or understatement of challenges and risks can have tangible impacts on the expectations of the general public, patient communities, and physicians and on the setting of health and science policies (Caulfield et al., 2016).

The Process

The process of revising and updating the ISSCR guidelines began at the 2014 annual ISSCR meeting in Vancouver, Canada, when the ISSCR board of directors empaneled a special task force. The task force of 25 scientists, ethicists, and experts in health care policy, with representatives from nine countries, was chaired by bioethicist Jonathan Kimmelman (McGill University). George Daley (Boston Children's Hospital) and Insoo Hyun (Case Western Reserve University), chairs of the guidelines task forces of 2006 and 2008, respectively, provided continuity and thematic consistency across the three ISSCR guidelines efforts.

The work of revisions fell most heavily upon a core steering committee comprised of Nissim Benvenisty, Timothy Caulfield, Helen Heslop, Charles Murry, Douglas Sipp, Lorenz Studer, and Jeremy Sugarman, who alongside Hyun, Daley, and Kimmelman served as co-chairs of working subgroups of the larger task force. Deliberations began in August 2014 with biweekly conference calls and face-to-face meetings in Boston and at the ISSCR Annual Meeting in June 2015 in Stockholm, when a draft version of the revised guidelines



Table 2. Number and Sources of Comments Received by the ISSCR on Draft Guidelines

Countries (Number of Comments Received)			
Argentina (1)	Australia (3)	Austria (1)	Brazil (1)
Canada (2)	China (1)	France (1)	Germany (5)
India (1)	Iran (1)	Italy (1)	Israel (1)
Japan (6)	Korea (1)	Netherlands (2)	Norway (1)
Singapore (1)	Spain (2)	Sweden (4)	Turkey (1)
United Kingdom (9)	United States (32)	Regional/International (7)	

Many comments represent the input from multiple individuals or entities.

Consortia, Societies/Networks, Organizations	
American Society for Reproductive Medicine	American Society for Transplantation
American Society of Transplant Surgeons	Associação Brasileira de Terapia Celular (Brazilian Association for Cell Therapy)
Australian Therapeutic Goods Administration	Austrian Society for Regenerative Medicine
California Institute for Regenerative Medicine	Canadian Institutes of Health Research
Catholic Organizations New York	Centre of Genomics and Policy at McGill University
Coriell Institute for Medical Research	European Medicines Agency
German Stem Cell Network	Health Research Authority, United Kingdom
Human Fertilization and Embryology Authority, United Kingdom	International Alliance of Patients' Organizations
International Society for Experimental Hematology	International Stem Cell Forum Ethics Working Party
International Society for Cell Therapy	Japanese Society for Regenerative Medicine
Korean Society for Stem Cell Research	Miltenyi Biotech
Nature Magazine/NPG	Organization for Economic Co-operation and Development
RUCDR Infinite Biologics	Secretariat on Responsible Conduct of Research, Canada
Spanish Agency on Medicines and Medical Devices	Stem Cell Network North Rhine-Westphalia

StemBANCC

Publication of the draft guidelines was announced widely and request for comment was made to 110 individuals/entities. Comments on the draft guidelines were received from a wide range of individual and organizational stakeholders from around the world. Comments were thoughtfully reviewed by the ISSCR task force. Listing does not constitute endorsement of the ISSCR Guidelines for Stem Cell Research and Clinical Translation.

was released. A three-month period of public comment followed, and targeted inquiries were made to a large number of individuals and organizations for feedback. The task force made particular efforts to solicit perspectives from diverse and underrepresented stakeholders. The taskforce also sought perspectives from individuals within regulatory authorities, funding agencies, industry, patient advocacy organizations, and professional societies. Ultimately, comments and critiques were received from 85 individuals and organizations, reflecting the seriousness with which the global community responded to the issuance of the draft guidelines (Table 2). All responses, including many in exhaustive detail, were cataloged, reviewed, and considered

by multiple members of the steering committee, with consultation from working group members on select issues. For the critical last phase of revision, the steering committee was supported by Sally Temple, ISSCR president-elect, who fostered additional communication with the society's executive committee and board of directors. In this final phase, issues flagged in review as contentious were weighed, debated, and reassessed by the working sub-groups and steering committee. After revising the draft released in Stockholm, a penultimate version of the guidelines document was then presented to the ISSCR board of directors at its meeting in December 2015. Following discussion and debate, the ISSCR board of directors voted unanimously to approve the revised



guidelines, which were then subject to extensive reformatting, referencing, and assembly of appendices into a final document, which we now release (ISSCR, 2016).

While we believe the 2016 ISSCR guidelines represent a considerably broader as well as more integrated set of principles and best practices to direct the review of both basic and clinical research protocols, we acknowledge that no guidelines can represent the final word. We appreciate that just as stem cell science and medicine have evolved over the last decade, new challenges will surface that necessitate an ongoing process of reflection, review, reinterpretation, and future revision. Such a contemplative and iterative process is healthy and essential to maintain a culture of adherence to sound ethical principles of research conduct. The 2016 ISSCR guidelines give confidence to practitioners and public alike that stem cell science can proceed efficiently and remain responsive to public and patient interests (Kimmelman et al., 2016b).

Finally, Paolo Bianco, a member of our task force who passed away suddenly and unexpectedly in November 2015, was a stalwart advocate for rigor in science and evidence-based clinical application. He was also a passionate and vocal critic of practitioners who violated the standards embodied in our guidelines. In recognition of Paolo's legacy, the task force has dedicated the 2016 ISSCR guidelines to his memory.

ACKNOWLEDGMENTS

The authors thank the many individuals and organizations who reviewed the draft guidelines and provided comments or otherwise contributed to our deliberations. Despite earnest efforts to digest and consider all feedback, we apologize for the errors that persist in the document, and invite ongoing comment. As a scientific advisor to the following companies, G.Q.D. receives consulting fees or holds equity in MPM Capital, Epizyme, True North, Solasia, Verastem, Raze, and 28/7. J.F.A. acknowledges the support of the Imperial NIHR-BRC. R.A.B. is an advisor to Living Cell Technologies for a New Zealand-based clinical trial. C.K.B. is the founder of LYST Therapeutics, received grant support from Gunze Limited, and is on the scientific advisory board for Cook Biomedical. H.E.H. is founder of Viracyte and holds a licensing agreement with Cell Medica and a collaborative research agreement with Celgene and Bluebird Bio. M.R. works as a consultant in the field of regenerative medicine and serves on the board and SAB of several companies. The opinions expressed by the author are solely his own and do not reflect the policy or work of the companies he is affiliated with. L.S. is a member of the Scientific Advisory Board of Neurona Therapeutics. J.S. is a member of the Bioethics Advisory Committee and Stem Cell Research Oversight Committee for Merck KGaA, for which he receives consulting income and reimbursement for travel expenses. M.T. has research funds from Healius and Sumitomo Dainippon Pharma. M.Z. is an employee of Viacyte, Inc.

REFERENCES

- American College of Obstetricians and Gynecologists. (2006). ACOG committee opinion no. 347, November 2006: using preimplantation embryos for research. *Obstet. Gynecol.* 108, 1305–1317.
- Caulfield, T., Sipp, D., Murry, C.E., Daley, G.Q., and Kimmelman, J. (2016). Confronting stem cell hype. *Science*. <http://dx.doi.org/10.1126/science.aaf4620>.
- Deglinerti, A., Croft, G.F., Pietila, L.N., Zernicka-Goetz, M., Siggia, E.D., and Brivanlou, A.H. (2016). Self-organization of the in vitro attached human embryo. *Nature*. <http://dx.doi.org/10.1038/nature17948>.
- ESHRE Taskforce on Ethics and Law. (2001). The moral status of the pre-implantation embryo. *Hum. Reprod.* 17, 1409–1419.
- Ethics Committee of American Society for Reproductive Medicine. (2013). Donating embryos for human embryonic stem cell (hESC) research: a committee opinion. *Fertil. Steril.* 100, 935–939.
- Haimes, E., Skene, L., Ballantyne, A.J., Caulfield, T., Goldstein, L.S., Hyun, I., Kimmelman, J., Robert, J.S., Roxland, B.E., Scott, C.T., et al. (2013). Position statement on the provision and procurement of human eggs for stem cell research. *Cell Stem Cell* 12, 285–291.
- Hyun, I., Wilkerson, A., and Johnston, J. (2016). Embryology policy: Revisit the 14-day rule. *Nature* 533, 169–171.
- International Society for Stem Cell Research (ISSCR). (2006). Guidelines for the conduct of human embryonic stem cell research. <http://www.isscr.org/docs/default-source/hesc-guidelines/isscrhescguidelines2006.pdf>.
- International Society for Stem Cell Research (ISSCR). (2008). Guidelines for the clinical translation of stem cells. <http://www.isscr.org/docs/default-source/clin-trans-guidelines/isscrgclinicaltrans.pdf>.
- International Society for Stem Cell Research (ISSCR). (2016). Guidelines for stem cell research and clinical translation. <http://www.isscr.org/guidelines2016>.
- Kimmelman, J., Heslop, H.E., Sugarman, J., Studer, L., Benvenisty, N., Caulfield, T., Hyun, I., Murry, C.E., Sipp, D., and Daley, G.Q. (2016a). New ISSCR guidelines on the ethics of stem cell research. *Lancet*. Published online May 11, 2016. [http://dx.doi.org/10.1016/S0140-6736\(16\)30390-7](http://dx.doi.org/10.1016/S0140-6736(16)30390-7).
- Kimmelman, J., Hyun, I., Benvenisty, N., Caulfield, T., Heslop, H.E., Murry, C.E., Sipp, D., Studer, L., Sugarman, J., and Daley, G.Q. (2016b). Global standards for stem-cell research. *Nature*. <http://dx.doi.org/10.1038/533311a>.
- Macklin, R. (1999). The ethical problems with sham surgery in clinical research. *N. Engl. J. Med.* 341, 992–996.
- Rettig, R.A. (2007). *False Hope: Bone Marrow Transplantation for Breast Cancer* (Oxford, New York: Oxford University Press).
- Shahbazi, M.N., Jedrusik, A., Vuoristo, S., Recher, G., Hupalowska, A., Bolton, V., Fogarty, N.M.E., Campbell, A., Devito, L.G., Ilic, D., et al. (2016). Self-organization of the human embryo in the absence of maternal tissues. *Nat. Cell Biol.* <http://dx.doi.org/10.1038/ncb3347>.



Smith, R.M., Schaefer, M.K., Kainer, M.A., Wise, M., Finks, J., Duwve, J., Fontaine, E., Chu, A., Carothers, B., Reilly, A., et al. (2013). Fungal infections associated with contaminated methylprednisolone injections. *N. Engl. J. Med.* *369*, 1598–1609.

Waring, M.J., Arrowsmith, J., Leach, A.R., Leeson, P.D., Mandrell, S., Owen, R.M., Pairaudeau, G., Pennie, W.D., Pickett, S.D., Wang, J., et al. (2015). An analysis of the attrition of drug candi-

dates from four major pharmaceutical companies. *Nat. Rev. Drug Discov.* *14*, 475–486.

Warmflash, A., Sorre, B., Etoc, F., Siggia, E.D., and Brivanlou, A.H. (2014). A method to recapitulate early embryonic spatial patterning in human embryonic stem cells. *Nat. Methods* *11*, 847–854.

Warnock, M. (1985). The Warnock report. *Br. Med. J. (Clin. Res. Ed.)* *291*, 187–190.