

ETHICS

The ISSCR Guidelines for Human Embryonic Stem Cell Research

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Human embryonic stem (ES) cells are valuable for biomedicine, but differing cultural, political, legal, and religious perspectives are potential barriers to international collaboration in this fledgling field. Recognizing the need for scientists to act transparently, to serve the public interest, and to preserve public trust, the International Society for Stem Cell Research (ISSCR) convened a task force to formulate guidelines for human ES cell research. The ISSCR guidelines were written by scientists, ethicists, and legal experts from 14 countries (1).

The ISSCR guidelines encompass the core values put forth by the Committee on Guidelines for Human ES Cell Research of the U.S. National Academy of Sciences (U.S. NAS) (2) and the Regulations of the California Institute for Regenerative Medicine (3), and acknowledge thoughtful governmental regulations already in place in several countries, particularly that of the Human Fertilisation and Embryology Authority of the United Kingdom (4). The ISSCR is the principal scientific society for stem cell scientists and transcends institutional, regional, and national political boundaries.

The ISSCR guidelines focus on research pertinent to derivation and use of pluripotent human stem cell lines and are not meant to encompass somatic (adult) stem cell research or human embryo or fetal tissue research. The ISSCR guidelines aim to facilitate international collaboration by encouraging investigators and institutions to adhere to a uniform set of practices. The ISSCR guidelines are subservient to all applicable laws and regulations of the country or region where the actual research takes place.

Major Principles

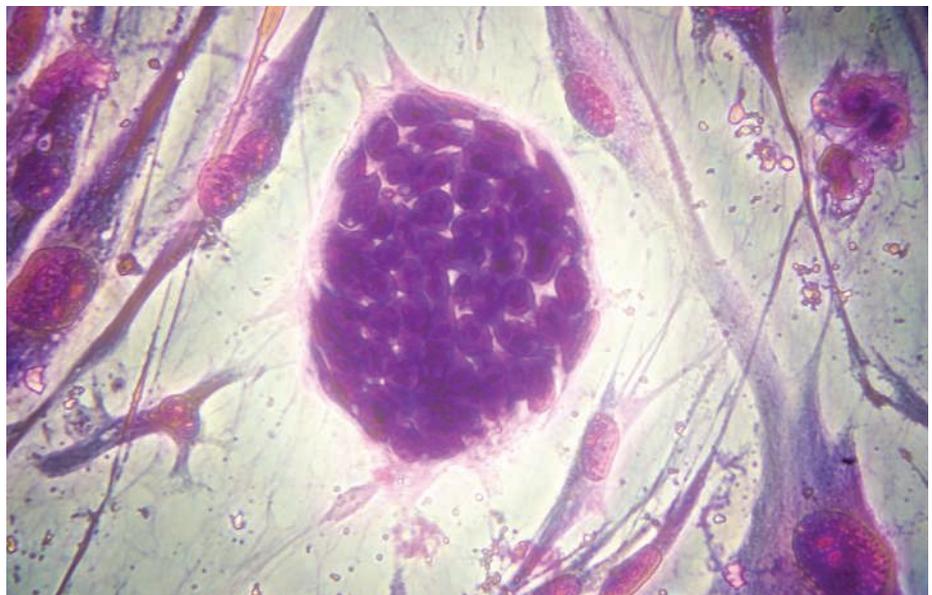
Call for oversight. Biomedical research is already subject to regulation and oversight. However, because human ES cell research raises unique and sensitive issues and requires specialized expertise to judge both scientific merit and ethical propriety, the ISSCR guidelines call for a specialized oversight process to complement existing institutional review

The International Society for Stem Cell Research describes major principles that should guide ethical stem cell research.

boards. In contrast to the U.S. NAS guidelines, which stipulated that institutions engaged in human ES cell research should form an ES cell research oversight (ESCRO) committee, the ISSCR guidelines do not specify the precise form of stem cell research oversight (SCRO). The ISSCR guidelines specify the key elements of a single rigorous review at the institutional, regional, national, or international level, thereby eliminating redundancy and allowing flexibility for varied oversight mechanisms in different countries.

Permissible and impermissible research. The ISSCR guidelines prohibit (i) all experiments that lack a compelling scientific rationale or raise strong shared ethical concerns—in particular human reproductive cloning; (ii) in vitro culture of human embryos beyond 14 days or the formation of the primitive embryonic streak; and (iii) the interbreeding of animals likely to harbor human gametes.

The “14-day limit,” first articulated in 1984 by the Warnock committee of the U. K. Human Fertilisation and Embryology Authority (5), is widely accepted by researchers in the human stem cell and fertility fields. It recognizes the significant biological distinctions between the earliest human embryos,



How can ethical principles for research encompass cultural differences? Shown is a human embryonic stem cell colony, on a background of mouse embryonic fibroblast feeder cells, stained with Wright-Giemsa to highlight the individual cells of the colony.

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which have not yet established even the most rudimentary rostral and caudal orientation (the primitive streak), and an embryo that has begun to initiate organogenesis. The U.S. NAS guidelines prohibit the mixing of cells of any nature with the pre-streak embryo. This restriction excludes a number of experiments considered standard in animal embryology, including cell aggregation studies to investigate the segregation of primitive embryonic blastomeres into inner cell mass and trophectoderm. Such experiments might yield insights into the origins of stem cells and might enhance the efficiency of ES cell derivation. The ISSCR Task Force reasoned that experiments with sound scientific rationale that respect the 14-day limit are permissible if they pass a thorough SCRO review.

The ISSCR guidelines diverge subtly from the U.S. NAS guidelines in restrictions placed on breeding of animals that might carry human gametes. Such experiments might be justified to investigate the consequences of tissue repair or regeneration on reproductive behavior or function, and they could be done with safeguards to prevent any inadvertent fertilization events (e.g., sterilization). The ISSCR guidelines place the onus on the SCRO process to evaluate permissibility of any particular experiment.

Experiments that are permissible only after SCRO review and approval include derivation of new lines or creation of animal chimeras, especially experiments likely to result in extensive chimerism of the brain or germ line. The ISSCR guidelines provide a means for excluding *in vitro* experiments with existing human ES cell lines from review, as appropriate, and exclude from SCRO review routine procedures that raise no appreciable moral concerns, such as assays of teratoma formation from human ES cell lines. Under the U.S. NAS guidelines, the teratoma assay requires ESCRO committee review because it entails the creation of a chimeric animal. We anticipate that other procedures may become exempt from SCRO review as the field evolves.

Requirement for explicit consent. For use of somatic cell nuclei in nuclear transfer experiments, the ISSCR guidelines call for obtaining contemporaneous and explicit consent from all somatic cell donors. Such a rigid requirement reinforces a position stated by the U.S. NAS guidelines to protect individuals who might not want their tissues unwittingly used in human ES cell research. For the research use of embryos generated with donated gametes, the ISSCR guidelines reaffirm the need for explicit consent from both gamete donors. In the future, informed consent for all

gamete donors should include the possible use of donated materials and their derivatives in human stem cell research.

Financial considerations. In some nations, like the United States, women who provide their eggs to infertile couples are routinely compensated—that is, provided money in addition to reimbursement of direct expenses—in a range that varies widely but is typically from \$2500 to \$5000 (6). Some believe that high payments may unduly induce women to ignore the risks of hormonal stimulation and surgical egg retrieval and thus may undermine the voluntary nature of women's choices to provide their eggs to infertile couples. Task force members had varied opinions on what financial accommodations should be allowed for donation of oocytes for research purposes. Some felt that altruism should be the only permissible motivation for research donation; others felt that asking women to bear the significant burden of time, effort, discomfort, and risk of donation without compensation was itself unfair and exploitative.

There was consensus for providing reimbursement of direct expenses incurred during the process of providing oocytes, although there was concern that even this financial consideration might invite abuse. The Task Force noted that healthy research volunteers who undergo invasive research procedures like bone marrow biopsy or colonoscopy are sometimes compensated, but could not reach consensus on the permissibility of even a modest honorarium for providing oocytes. The Task Force concluded that research and ethical review committees are experienced in evaluating financial considerations and that substantial literature documents their ability to distinguish undue inducements from payments that appropriately acknowledge the interests of the subject (7–10). Thus, the Task Force agreed to allow the SCRO process to determine the financial considerations involved in egg procurement, guided by the principle that “there must be a detailed and rigorous review to ensure that reimbursement of direct expenses or financial considerations of any kind do not constitute an undue inducement.”

Encouraging compliance. To encourage adoption of the ISSCR guidelines by the research community, and as a mechanism of enforcement, the guidelines call for journal editors and granting agencies, as a stipulation for publication or funding, to require investigators to attest to compliance with the ISSCR guidelines or an equivalent set of regulations. To set the guidelines into practice, sample informed-consent documents for the procurement of human research materials were cre-

ated and subjected to extensive peer review by an external international group of ethicists, research policy experts, and leaders of institutional review boards and ES cell research oversight committees. These documents encompass the principles articulated in the ISSCR guidelines and are available from the ISSCR Web site (11). The ISSCR hopes to establish a database of human ES cell lines that have been derived in accordance with the ISSCR guidelines.

Finally, the ISSCR guidelines state that researchers engaging in human ES cell research must make their materials readily accessible to the biomedical research community. The guidelines thus include recommendations for the derivation, banking, storage, and distribution of research materials, and provide a sample Material Transfer Agreement to facilitate exchange of research materials (11).

The Future

The ISSCR leadership is committed to ongoing review and revision of the guidelines, and appreciates that new research in science, ethics, law, and policy will challenge us with new questions. We are hopeful that the many communities affected by and attentive to stem cell research will consider these guidelines a call for their robust participation in the processes that decide the direction of research. The ISSCR seeks the support of its membership, members of other scientific societies, our institutions, and the public to promote adoption of the ISSCR guidelines globally.

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- See SOM for conflict-of-interest statements.

Supporting Online Material

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