Stem Cell Reports

and members of the public, including patients. A summary of the key updates and issues is presented here.

OVERVIEW OF THE GUIDELINES EVOLVING WITH THE SCIENCE

With any area of research, especially when it relates to humans and involves issues that may be considered ethically contentious, it is important to ensure it is subject to appropriate review and oversight. The stem cell field is one such area, and while some countries have relevant laws and policies governing how research and clinical applications are conducted, many jurisdictions around the world do not or they have legislation with substantial gaps and ambiguities. Given this, carefully constructed guidelines can play a critical role for scientists and clinicians conducting research and treating patients; for the public who may have hopes for or concerns about the research, may be funding it, and may become recipients of any treatments that result from it; and for governments that may have other more pressing demands on their capacity to develop laws and policies and establish institutions to support them.

The International Society for Stem Cell Research (ISSCR) was founded in 2002 and rapidly grew to become the preeminent global, science-based organization dedicated to all aspects of stem cell research and its clinical translation. In addition to its role as a member-based organization to promote scientific discourse and the sharing of data, early on the Society decided it should undertake the responsibility for developing guidelines to encourage high standards in practical and ethical aspects of relevant research and its applications.

The first ISSCR Guidelines, published in 2006, had a major focus on human embryonic stem cells (hESCs), which had first been derived only 8 years earlier (Daley et al., 2007). By 2006, numerous hESC lines were being used by researchers in many countries, with substantial variation in both methodology and in the way their derivation and use was regulated. The 2006 Guidelines built upon the experience with earlier, more local efforts, reflecting underlying ethical principles for research, and proposed that institutions should establish stem cell research oversight (SCRO) committees. This was important to give regulators and the public confidence that hESC lines were being derived and used both sensibly and with sensitivity.

In 2008, the ISSCR issued Guidelines focused on the clinical translation of stem cell therapies, essential if these were to realize their potential for regenerative medicine. Then, in 2016, the ISSCR updated and combined the previous two Guidelines, incorporated research and uses of induced pluripotent stem (iPS) cells, articulated ethical principles for stem cell research (such as integrity of the research enterprise, respect for patients and research subjects, and social and distributive justice), and expanded the purview to include research involving human embryos (Daley et al., 2016; Hyun et al., 2008). At the time, the latter was justified by the following: "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 … human embryo research … may not explicitly pertain to stem cells or stem cell lines, such as single cell analyses, genome modification, and embryo chimerism" (Daley et al., 2016). The 2016 Guidelines also proposed that, depending on the nature of the experiments to be conducted, review should entail a renamed "Embryo Research Oversight (EMRO)" process, signaling this wider remit.

Over the last 5 years, there have been several key developments in the science related to the biology of stem cells and human embryos and to their potential and actual uses, including the application of genome editing, as well as an increase in examples of appropriate and inappropriate clinical applications. The pace, extent, and potential importance of the new developments, and how they affect one other, have demanded a substantial rewrite and expansion of many sections of the ISSCR Guidelines, a two-year collaboration with international experts and respected leaders in areas of stem cell science, ethics, and law (Box 1). Key advances that the new 2021 Guidelines cover include the following: the culture of human embryos and stem cell-derived models of embryo development, both embryo-like entities and specific organ-like structures (organoids); chimeras; *in itro* gametogenesis iobus51.6(with)-7(extent,)1subs3pies, esmbig5yo 2016.

such as those of openness, transparency, fairness, and equitable access to new therapies. This has also necessitated a fresh look at mechanisms ensuring appropriate review and oversight of research and clinical applications, where the Guidelines now place greater emphasis on the considerations that should be addressed rather than on specific committees.

SCIENTIFIC AND ETHICAL REVIEW

Robust mechanisms of review and oversight are essential to develop and maintain confidence in research and its applications. These help to ensure best practice with respect to the science and ethics, including obtaining informed consent from donors and patients. The updated Guidelines maintain rigorous independent review for human stem cell and embryo research, and for related research activities, but provide additional clarity, criteria, and practical guidance for its oversight. To emphasize both the purpose of the review and how it must be capable of evaluating the unique aspects of the science and the associated ethical issues of the research, along with broader concerns, the revised Guidelines now refer to it simply as a "specialized scientific and ethics oversight process." They indicate that the review can take place at the institutional, local, regional, or national level but encourage mechanisms to ensure consistency wherever possible. Moreover, although the Guidelines no longer recommend any specific named committee or process, they propose that it should be conducted by an established body, including an EMRO, ESCRO, SCRO, or other committee, as long as this includes the relevant expertise appropriate for the topic being reviewed, as well as having generalists and lay members.

As in previous iterations, the review process proposes several categories covering both research and its applications, but to accommodate advances in science and changing views, the Guidelines now subdivide some of these (see also Box 2).

Category 1, which previously captured research exempt from review, now has two subcategories: 1a and 1b.

1A includes research determined to be exempt from a specialized scientific and ethics oversight process after being assessed by the appropriate existing mandates and committees for laboratory research. This includes the routine culture of pluripotent stem cell lines, the reprogramming of human somatic cells, and research on stem cell culture systems that model specific stages of development or specific anatomic structures including organoids. Of course, as with all research actively involving the acquisition of human cells or tissues, appropriate consent must first be obtained from the donor or their legal representative.

1B is a new sub-category that includes types of research that need to be reported to the entity responsible for the specialized scientific and ethics oversight process, but at the discretion of this entity and subject to regulations and policies in the relevant jurisdiction, the research need not normally be subject to further or ongoing review. This covers projects that may be of no public concern in themselves but that have the potential to lead to work that might, such as *in itro* chimeric embryo research and *in itro* gametogenesis where there is no intent to generate a human embryo.

The principles covering review under Category 2 remain the same; however, this now includes additional types of research. It is research under this category that will clearly give the majority of work for the specialized scientific and ethics oversight process (see Box 2). It includes research that the process might conclude is permissible, perhaps with conditions applied, and as long as it also complies with regulations and policies in the relevant jurisdiction.

Category 3, as before, is concerned with types of research that are prohibited. However, it has now been revised and subdivided into two categories to make a distinction between the reasons for prohibition.

may eventually prove to be a close resemblance to the latter, they are very unlikely to possess typical epigenetic marks and may miss specific cell states required for viable embryogenesis. In addition, because they are derived from stem cell lines, this allows generation of many genetically identical blastoids, which has experimental advantages; but this would be another potential route to "human reproductive cloning," which is not permissible for any reason. Thus, transfer to a human or animal uterus is not permitted (Category 3B). Nevertheless, such models might well reduce the need for genuine human embryos in some types of research. More detailed discussion of embryo culture and embryo models can be found in the white paper by Clark et al. elsewhere in this issue (Clark et al., 2021).

more because they might be of public interest rather than their raising unique ethical concerns. A recent example of this involved introducing "expanded potential" human pluripotent stem cells into macaque blastocysts that were then cultured to primitive streak stages, where they showed a modest contribution (Tan et al., 2021). If such experiments involved the transfer of the embryos into the uterus of a non-human animal, this would fall under Category 2 because it would clearly demand consideration by the special review and oversight process (although this would exclude transfer into greater and lesser apes, which is prohibited). A particular concern arises if there were a substantial contribution of human cells to the CNS of the animal. It will be difficult to predict how brain size and connections to animal sensory and motor systems will affect phenotypes. Therefore, such experiments should proceed in a careful stepwise manner, with review at critical stages, paying particular attention to behavior and animal welfare issues if any of the chimeras are brought to term (National Academies of Sciences, Engineering, and Medicine, 2021). Finally, transfer of such chimeras into a human uterus or breeding chimeric animals where there is a chance they have human gametes are prohibited and clearly fall into Category 3B. For more about this topic and the discussions around it, please see Hyun et al. (2021) in this issue.

Mitochondrial replacement techniques

Mitochondrial replacement techniques (MRTs) involve the transfer of nuclear genetic material, notably the meiotic spindle with chromosomes attached before fertilization or both the maternal and paternal pronuclei at the zygote stage after fertilization, into an enucleated oocyte or zygote at the equivalent stages. (A third method, polar body transfer, might also be feasible, but published data on this are limited.) This has the effect of swapping the cytoplasm, which contains the mitochondria with their DNA (mtDNA), in order to effectively replace pathogenic mtDNA's causing serious disease with normal mtDNA. This should allow a woman (mitochondria are only inherited via the mother) at risk of having an affected child to have a genetically related child free from mitochondrial disease. The child would have contributions as normal from the mother's nuclear DNA as well as that from the father, but mtDNA from the oocyte donor. To date, the the UK is the only country to actively permit in law the use oc449(-256.510r)71.ut-201.speciafially o1(ntoc)TJ34TJan

proceed with clinical use of the methods will be dependent not only on substantial preclinical assessments as to safety, efficiency, and efficacy, but also on appropriate policies, regulation, and oversight being in place. It will also require meaningful public engagement, political support, and proper oversight within the relevant jurisdiction.

The commission report provides guidance for initial clinical uses of human germline genome editing once the technical, safety, and ethical issues are resolved, including a case-by-case evaluation of scientific methods and the societal and ethical issues associated with any proposed use. The revised ISSCR guidelines also encourage the development of a comprehensive regulatory and ethical framework for overseeing heritable human genome editing that builds on the existing regulatory frameworks for new biotechnologies, the practice of medicine, and describes a set of principles that should be followed. The report from the WHO's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, which is due to be published in May 2021, provides a framework for governance, as well as other material that should be of benefit when considering not just heritable human genome editing, but also somatic genome editing (see below).

Non-heritable (non-reproducti e) germline genome editing. It follows that preclinical research to optimize methodologies and minimize potential harms associated with any heritable application is encouraged. Such research, if it involves human embryos (either surplus embryos from IVF that are not wanted for reproduction and have been donated for research, or embryos that are created specifically for research), would be placed in Category 2 and subject to robust review and oversight, as would any basic research involving human genome editing to explore, for example, the role of specific genes during early embryogenesis. The use of other germline cells for this research, notably pluripotent stem cells and gamete progenitors, including spermatogonial stem cells, would fall under Category 1A or 1B, respectively, unless these were being used to create embryos, in which case it would move to Category 2.

Somatic genome editing. The Guidelines also provide new guidance on somatic genome editing research and applications, including *in utero* genome editing and stem cell-based interventions. Notably, clinical research involving *in utero* stem cell-based interventions or genome editing involves two patients, the pregnant woman and the future child, and should be undertaken, preferably in the context of a well-designed clinical trial, only when it offers the prospect of a benefit greater than that of post-natal interven-

The Guidelines also stress that any review and oversight process must ensure that vulnerable individuals and populations are not exploited. There must be no undue inducements or other unacceptable influences for the provision of human cells and tissues. In addition, the Guidelines recommend that cell and tissue donors should be able to choose whether they wish to receive incidental findings, such as the presence of a risk allele for a genetic disease or cancer, and that this should be clear in the consent process. Provenance of stem cell lines must be easily verifiable by access to relevant documents such as material transfer and licensing agreements and data demonstrating the identity of the cell line and uses allowed under the original informed consent (Isasi et al., 2019). However, due to advances in and increasing ubiquity of genomic sequencing, researchers are strongly encouraged to maintain confidentiality when sharing genomic data that has the potential to connect donors and family members with de-identified cells and tissues (Isasi et al., 2014; Knoppers et al., 2011).

Overall, the revised Guidelines provide more realistic recommendations on the derivation and banking of new lines that will protect donors, facilitate research by making it clearer what is permitted or not, and ease compliance for companies developing stem cell-based products.

CLINICAL TRANSLATION

The number of clinical trials and other interventions involving stem cells has increased significantly over the last 5 years, as have the number of inappropriate uses and exaggerated or false claims. Given the knowledge gained regarding what works well, what might not, and what is lacking, considerable effort was taken to modernize the recommendations for clinical translation and regulator approval in the revised Guidelines.

To facilitate bona fide treatments, the Guidelines now include a new recommendation on sex as a biological variable (although this must apply also to basic and preclinical research), support the use of accelerated approval pathways based on surrogate or intermediate endpoints, encourage robust post-market surveillance systems in jurisdictions with conditional approval pathways, and encourage health systems and payers to establish a process for evaluating the health benefits and economic value of stem cell-based interventions.

New or updated recommendations are also made in the Guidelines to curb premature or inappropriate commercialization of cell therapies; consequently they include an updated recommendation to forcefully caution against the premature commercialization of unproven stem cell-based interventions. They also adopt international standards for defining stem cell-based products as drugs or advanced therapy medicinal products (ATMPs) if such products have been substantially manipulated or are provided for non-homologous uses; this standard aligns with the US FDA, the EMA, and Australia's TGA). They include new recommendations on regulations authorizing stem cell-based products, including the demonstration of substantial evidence of effectiveness in appropriately powered, well-controlled clinical trials, with statistically significant findings. They narrow the types of stem cell-based products eligible for the medical innovation pathway that is aligned with international regulatory standards, including the US FDA. Finally, they strengthen the recommendation on patient registries to clarify their use as a tool for disease histories and tracking long-term patient outcomes. The recommendation also notes that registries are not adequate substitutes for randomized controlled trials to demonstrate the safety and efficacy of products for marketing authorizations. Indeed, in some cases the registries seem to be used merely as a form of advertising, a practice that is at best misleading and goes against a duty of care for patients.

CONCLUSIONS

It is hoped that these revised Guidelines are sufficiently forward looking to capture the science surrounding human stem cell and embryo research and its social and regulatory context, not just now, but also its likely trajectory over the next several years. It is notoriously difficult to predict how any of these might change and over what time scale. This has been evident over the last 5 years, with many advances and altered opinions necessitating an extensive set of revisions. Neither the field nor those involved in it should remain static; consequently, the Guidelines will need to evolve and should be read with this in mind. Nevertheless, the principles underlying the Guidelines, which have not changed from earlier versions, will endure. Therefore, whether carrying out research or treating patients, adhering to these principles should always be the priority.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2021.05.012.

DECLARATION OF INTERESTS

R.L.-B. has no financial conflicts to declare. R.L.-B. serves on the following advisory boards: Scientific and Clinical Advances Advisory Committee of the Human Fertility and Embryo Authority; Sense About Science, Member of Board of Trustees; Public Library of Science (PLOS), Board Member, Chair of Audit Committee, Chair of Remunerations Committee, and member of Scientific Advisory Board; Royal Society, Chair of "Genetic Technologies

Programme," Progress Educational Trust, Chair of the Board of Trustees; member of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing; Chair of ISSCR Task Force to Update the Guidelines; and member of External Advisory Board, "Cambridge Reproduction Strategic Research Initiative," University of Cambridge, UK.

R.B. receives funding from UK NIHR, MRC, Wellcome, Cure Parkinson's Trust, and EU. R.B. received funding from Parkinson's UK, CHDI, Rosetrees Trust, and Evelyn Trust. R.B. receives royalties from Wiley and Springer and also has an ongoing consultancy role for the following companies: Novo Nordisk, UCB, Aspen Neuroscience, and BlueRock Therapeutics.

A.H.B. is a co-founder of OvaNova, Inc., as well as a co-founder of Rumi Scientific, Inc.

R.A.C. is Professor Emerita, University of Wisconsin; David Hamburg Fellow, Nuclear Threat Initiative; and Lead Co-Chair, BioMADE. R.A.C is a member of the WHO Expert Advisory Group on Genome Editing; member of the Planning Committee, Third International Summit on Genome Editing; and Co-Chair of the US National Academy of Medicine committee on emerging sci-9.9(of)-290.3(Extern2or)-192(352.4(Cha14chnoln22.7(')-490.3TJT*(IR438)-3ng)-34-4