ISSCR GUIDELINES FOR STEM CELL RESEARCH AND CLINICAL TRANSLATION: THE 2021 UPDATE

Robin Lovell-Badge[1*#], Eric Anthony[2], Roger A. Barker[3], Tania Bubela[4], Ali H. Brivanlou[5], Melissa Carpenter[6#], R. Alta Charo[7#], Amander Clark[8#], Ellen Clayton[9], Yali Cong[10], George Q. Daley[11#], Jianping Fu[12], Misao Fujita[13], Andy Greenfield[14], Steve A. Goldman[15], Lori Hill[16], Insoo Hyun[17#], Rosario Isasi[18], Jeffrey Kahn[19], Kazuto Kato[20], Jin-Soo Kim[21], Jonathan Kimmelman[22], Jürgen Knoblich[23#], Debra Mathews[19], Nuria Montserrat[24], Jack Mosher[2], Megan Munsie[25], Hiromitsu Nakauchi[26], Luigi Naldini[27], Gail Naughton[28], Kathy Niakan[1,29], Ubaka Ogbogu[30], Roger Pedersen[31], Nicolas Rivron[32], Heather Rooke[33#], Janet Rossant[34#], Jeff Round[35], Mitinori Saitou[13], Douglas Sipp[36#], Julie Steffann[37], Jeremy Sugarman[19], Azim Surani[38], Jun Takahashi[13], Fuchou Tang[10], Leigh Turner[39], Patricia J. Zettler[40], Xiaomei Zhai[41]

Francis Crick Institute, UK[1]; International Society for Stem Cell Research[2], Cambridge Center for Brain Repair and WT-MRC Stem Cell Institute, UK[3]; Simon Fraser University, Canada[4]; The Rockefeller University, USA[5]; ElevateBio/Carpenter Group Consulting, USA[6]; University of Wisconsin, USA[7]; University of California, Los Angeles, USA[8]; Vanderbilt University, USA[9]; Peking University, China[10]; Harvard Medical School, USA[11]; University of Michigan, USA[12]; Kyoto University, Japan[13]; MRC Harwell Institute, UK[14]; University of Rochester Medical Center, USA and the University of Copenhagen (Denmark)[15]; MD Anderson, USA[16]; Case Western Reserve University School of Medicine and Harvard Medical School, USA[17]; University of Miami, USA[18]; Berman Institute of Bioethics, Johns Hopkins University, USA[19]; Osaka University, Japan[20]; Seoul National University, Korea[21]; McGill University, Canada[22]; IMBA-Institute of Molecular Biotechnology, Austria[23]; Institute for Bioengineering of Catalonia (IBEC), Spain[24]; University of Melbourne, Australia[25]; Stanford University, USA/University of Tokyo, Japan[26]; Università Vita-Salute San Raffaele, Italy[27]; Histogen, USA[28]; Centre for Trophoblast Research, University of Cambridge, UK[29]; University of Alberta, Canada[30]; Stanford University, USA[31]; IMBA-Institute of Molecular Biotechnology, Austria[32]; Broad Institute, USA[33]; Gairdner Foundation/SickKids, Canada[34]; Institute of Health Economics, Canada[35]; RIKEN Center for Developmental Biology, Japan and Keio University School of Medicine, Japan[36]; Université Paris Descartes, France[37]; Gurdon Institute, University of Cambridge, UK[38]; University of Minnesota, USA[39]; Ohio State University, USA[40]; Peking Union Medical College, China[41]

*Corresponding author: Robin.Lovell-Badge@crick.ac.uk

[#]ISSCR Task Force to Update the Guidelines Steering Committee

ABSTRACT: The International Society for Stem Cell Research has updated its Guidelines for Stem Cell Research and Clinical Translation in order to address advances in stem cell science and other relevant fields, together with the associated ethical, social and policy issues that have arisen since the last update in 2016. While growing to encompass the evolving science, clinical applications of stem cells, and the increasingly complex implications of stem cell research for society, the basic principles underlying the Guidelines remain unchanged, and they will continue to serve as the standard for the field and as a resource for scientists, regulators, funders, physicians, and

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

eTOC:
The updated Guidelines for Stem Cell Research and Clinical Translation describe the ethical principles and best practices for basic, translational, and clinical research involving stem cells and human embryos. The updated Guidelines include new recommendations to address the recent scientific advances involving embryos, stem cell-based embryo models, chimeras, organoids, and genome editing.

I. 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 organisation 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, which 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 realise 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 (Hyun et al., 2008; Daley et al., 2016). At the time, the latter was justified by: “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 five years, there have been several key developments in the science related to the biology of stem cells and human embryos, 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. Key advances that the new 2021 Guidelines cover include: 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 vitro* gametogenesis from cells; mitochondrial replacement techniques; somatic and germline genome editing; enhanced guidance for procurement of stem cell lines; and more robust clinical translation guidance (Isscr.org/guidelines). These new developments justify even more the inclusion of embryo research within the Guidelines, especially as ESCs or iPSC can provide both a test of methodology before moving to embryos and ESCs can provide subsequent tests of safety and efficacy. Moreover, while the 2021 ISSCR Guidelines have evolved most clearly with respect to the underlying science, it also reflects evolving attitudes to what might be permissible, both in research and possible clinical applications, as well as to the importance of certain values, 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.

II. 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 emphasise 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 Table 1):

Category 1, which previously captured research exempt from review, now has two subcategories:

1a: 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: This is a new sub-category, which 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 vitro* chimeric embryo research and *in vitro* gametogenesis where there is no intent to generate a human embryo.

Category 2. The principles covering review under this category 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 Table 1). 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:

3a: Research activities currently not permitted because the approaches are not yet considered safe enough and/or raise ethical issues that are unresolved. Examples include research on human germline genome editing, mitochondrial genome editing, and the use of human gametes differentiated from human stem cells for fertilization and human reproduction.

3b: Prohibited research activities that should not be pursued because of broad international consensus that such experiments lack a compelling scientific rationale and are widely considered to be unethical. This category includes human reproductive cloning, breeding chimeras that may contain human gametes, and transfer of human embryos to an animal uterus, among other lines of research.

III. NOTABLE NEW GUIDANCE

(i). Embryo culture and embryo models

Two papers were published in 2016, around the time the previous version of the Guidelines was published, showing that it was possible to culture intact preimplantation human embryos up to the equivalent of 13-day post-implantation embryos, i.e. shortly before gastrulation which begins around 14 days in humans (Shahbazi et al., 2016; Deglincerti et al., 2016). The methods were based on those developed about two years earlier for mouse embryos, with evidence that these could undergo gastrulation. It has been possible to culture macaque embryos up to about 20 days, well beyond the 14-day equivalent and gastrulation in human embryos (Niu et al., 2019; Ma et al., 2019). This has not been done with human embryos, because of the "14-day rule" that has been adopted in some guidelines, including those from the ISSCR, and enshrined in law in several countries, such as in the UK since 1990. There is now building pressure to extend or even abolish this limit in order to permit research into very important stages of human embryo development, about which we know little, but where many cases of miscarriage or birth defects are likely to have their origins (Williams and Johnson, 2020; Hyun et al., 2021; McCully, 2021). Other reasons for extending the culture period include: (i) To provide control material against which to validate stem cell-based embryo models (see below), which, if successful, would reduce the future need to carry out some types of research directly with human embryos; and (ii) to enable more thorough analysis of safety and efficacy of a wide range of methods either currently employed in IVF or that could be introduced, notably mitochondrial replacement techniques, heritable human genome editing, and *in vitro*-derived gametes (see below) (Clark et al., 2021).

Consequently, the *in vitro* culture of any intact human preimplantation embryo beyond 14 days or formation of the primitive streak (whichever occurs first) is now removed from Category 3. Instead, all research involving culture of intact human embryos is subject to Category 2 review, but balancing the potential value of this research with the ethical and societal concerns raised by it, and taking into account the social responsibility to be transparent throughout the process, the guidelines recommend that before a committee responsible for the specialized scientific and ethics review process may even consider applications for human embryo research beyond formation of the primitive streak or 14 days, national academies of science, academic societies, funders, and regulators should lead public conversations on the scientific significance as well as the societal, moral, ethical and policy issues raised by allowing such research (Recommendation 2.2.2.1). This public dialogue should help provide guidance on what types of experiments might prove permissible.

One of the guiding principles of the review process with respect to human embryos is that there should be no valid (and existing) alternative way of obtaining the same information. This leads to the topic of embryo models. In parallel to the development of embryo culture systems, stem cell-based embryo models have rapidly advanced since the 2016 Guidelines and two distinct types are now recognized by the new Guidelines:

(a) *Non-integrated models (Category 1b)*: These experimentally recapitulate some, but not all, aspects of the early postimplantation embryo, and would include gastruloids. These lack extraembryonic cells types and may have only a partial anterior-posterior embryonic axis and would therefore have no reasonable expectation of achieving substantial development *in vitro*, *or in vivo* if any attempt was made to transfer them to a human or animal uterus. These were previously part of Category 2 when no distinction was made between non-integrated and integrated models.

(b) *Integrated model*s (*Category 2*): These models, which include 'blastoids' derived entirely from stem cell lines, contain relevant embryonic and extra-embryonic cell types, and could potentially achieve the complexity by which they might realistically undergo further integrated development if cultured for additional time in appropriate conditions or, theoretically, if transferred to a uterus. After review by the specialized scientific and ethics oversight process, and if permission is given, these could be maintained in culture for the minimum time necessary to achieve the specific scientific objectives. Any absolute time limit, such as 14 days, would not make sense, in part because these entities would already have had an extended period in culture as stem cells, but also because they are not *bona fide* embryos. Despite what 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).

(ii). *In vitro*-derived gametes

While not yet achieved, there has been notable progress in research aimed at generating functional gametes from stem cells, either entirely *in vitro* or after a combination of *in vitro* culture followed by incorporation into gonads or gonadal-like structures *in vivo*. This progress is most pronounced with animal models, notably mice, where *in vitro*-derived sperm or oocytes have been obtained using directed differentiation of pluripotent stem cells followed by co-culture with testicular or ovarian cells, respectively, or in a range of mammals from the mouse to macaques, where spermatogonial stem cells can be cultured, genetically manipulated, and then introduced into the testis to undergo spermatogenesis. Moreover, at least a proportion of gametes derived using these protocols have been shown to be capable of giving rise to zygotes after fertilization and then to embryos and live born animals. There are many reasons for trying to achieve this in humans, notably: (i) As a way to research and understand human germ cell and gamete development, which has been very difficult to study; (ii) As a means to restore fertility, e.g. after cancer radiotherapy or chemotherapy; (iii) To provide a supply of gametes, notably oocytes, for a wide range of studies on early embryos, reducing the need for gamete donors; and (iv), to provide a route to heritable human genome editing (see below). The revised Guidelines hold that research conducted *in vitro* involving the derivation of human sperm or oocytes can proceed without review by a specialized oversight process, as long as no attempt is made to fertilize them or otherwise create embryos. However, because of the likely interest and concern from both the public and regulators, this research has been placed in Category 1B. If, however, the research entails testing gametes derived after any period of *in vitro* culture by fertilization and/or the creation of embryos, this must be subject to review, approval, and ongoing monitoring, as appropriate, through a specialized oversight process capable of evaluating the unique aspects of the science and the associated ethical issues. This latter research is therefore firmly in Category 2.

(ii). Organoids

Methods to derive and culture specific cell types, tissues and organoids from stem cells have also improved since 2016, with a greatly expanded repertoire of sometimes quite sophisticated structures now being studied. Most of these raise few ethical concerns. However, extensive coverage of the topic by the media prompted discussions during the process of revising the Guidelines whether work using central nervous system (CNS) organoids warranted review through the specialized oversight process. These discussions included the question of whether CNS organoids may achieve consciousness or perceive pain. However, at this time, there is no biological evidence to support such concerns. Both require a level of complexity and maturity, and connections with relevant sensory systems, that are not achieved in any current culture system. Consequently, all organoid research is currently in Category 1A. Nevertheless, the ISSCR and future Guidelines update committees should review this topic as science advances and additional information becomes available (National Academies of Sciences, Engineering, and Medicine, 2021).

(iii). Human-Animal chimeras

There are many reasons why it can be useful to generate animals containing human cells or tissues. These notably include assaying the potential of human stem cells in an *in vivo* situation; creating better animal models for studying human disorders and ways of treating these; and even perhaps the generation of organs and tissues for transplantation. This is a complex area where concerns vary according to type and stage of non-human animal used as recipient/host and the specifics of the human cells, notably whether they have a broad or narrow potential (which may only be discovered on carrying out the experiments). Additional methods, such as 'blastocyst complementation' can also be used, at least in theory, to allow human cells introduced into early embryos to completely replace a specific tissue or even, perhaps, to confine their likely contribution to only this tissue in the resulting animal. As with other methods outlined in this article, there have been significant advances made over the last five years in making and analysing such chimeras, and these are very likely to continue apace.

Relevant areas of potential research fall into almost all of the review Categories. If the experiment involves the transfer of a few stem cells into a postnatal animal, then this would not require any special review outside that provided for animal research generally; i.e. it would be Category 1A. Chimeric embryo research in which pluripotent human stem cells are transferred into mammalian non-human embryos and cultured *in vitro* would be Category 1B. This is a new requirement making these experiments reportable, more because they might be of public interest, rather than them 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 step-wise manner, with review at critical stages, paying

particular attention to behaviour 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.

(iv). Mitochondrial replacement techniques

Mitochondrial replacement techniques (MRT) 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 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 of MRT specifically to avoid serious mitochondrial disease. Regulations were passed in 2015 by the UK Parliament and detailed guidelines were then drawn up and adopted by the regulator, the Human Fertilisation and Embryology Authority (HFEA), who granted the first licence to carry out the procedures to researchers in Newcastle in 2017. However, the techniques are now being used elsewhere, and not just to avoid mitochondrial disease, but as a way to overcome female infertility where preimplantation embryos generated by *in vitro* fertilisation (IVF) repeatedly fail to develop. There is no established explanation for why MRT should work for the latter women, therefore application of these methods in such cases is speculative. The revised Guidelines therefore limit the clinical use of MRT to those at high risk of transmitting serious mtDNA-based diseases to their offspring and when no other treatments are acceptable. Such use now falls under Category 2, whereas previously MRT was in Category 3. Due to inadequate pre-clinical data and scientific rationale, the Guidelines also recommend not using MRT for unexplained female infertility associated with poor oocyte/embryo quality. Notably, the Guidelines also encourage more research to refine and assess the safety and efficacy of MRT, in particular to address a potential problem of 'reversion', which was seen in preclinical data involving the culture of ES cells derived from MRT embryos, where the maternal mtDNA may come to predominate again (Greenfield, et al., 2017)

(v). Genetic alteration of the mitochondrial genome (mtDNA)

Genome editing of mtDNA provides another approach to allowing women at risk to have a genetically-related child free from mitochondrial disease. This could be done in addition to the use of MRT to eliminate the possibility of any carryover of the abnormal mtDNA, by simply cutting and destroying the maternal mtDNA haplotype; or it could be carried out as an alternative, either to reduce the proportion of mutant mtDNA in cases of heteroplasmy or to correct the relevant sequence in the mtDNA. Research involving editing of mtDNA in human embryos would be

permitted under Category 2, however, transferring them into a human uterus for gestation is currently not permitted. The latter is placed in Category 3A because there is scientific rationale behind this possible approach, but as yet insufficient preclinical data regarding safety and efficacy; indeed, in countries with relevant legislation, this is currently illegal. Ideally, there would also need to be demonstrable public support to use the methods clinically in any jurisdiction contemplating clinical use of these methods, which would be a form of heritable genome editing, albeit of the mitochondrial and not nuclear genome.

(vi). Human genome editing

(a) **Heritable genome editing (or germline genome editing for reproductive purposes).** This remains a prohibited research activity, because currently the methods are neither sufficiently safe nor efficient. However, because there are defensible reasons for pursuing this line of research, this has been placed in Category 3A. These reasons may include situations where correcting a deleterious gene variant is the only way that prospective parents may have a genetically-related child (see the Commission Report from the National Academy of Medicine, National Academy of Sciences, and the Royal Society, 2020). However, any decision to 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).

(b) **Non-heritable (non-reproductive) 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, when it would move to Category 2.

(c) **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 interventions, does not pose excessive risk to the pregnant woman, and where there is institutional capacity for autopsy (in the case of miscarriage or stillbirth) or follow-up (in the case of live birth).

Basic and preclinical research on somatic genome editing, which is conducted *in vitro* and/or in animal models, should not require specialised review and oversight and falls into Category 1A. Clinical research and applications of somatic genome editing should largely be covered by existing review and oversight mechanisms governing gene therapy (Doudna, 2020). However, detailed and additional considerations are provided within a new Appendix to the ISSCR Guidelines. The WHO's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing also considers somatic genome editing. It does so because, as well as offering potential treatments, applications of somatic genome editing could be open to abuse and malpractice, and the topic also raises issues of social and distributive justice. The WHO Committee's Report should again provide an authorative reference point for considering governance in this area.

IV. PROCUREMENT OF CELLS AND TISSUES / DERIVATION OF STEM CELL LINES

The revised ISSCR Guidelines provide a new three-tiered system to streamline the review process for the procurement of banked and historical cell lines, while maintaining a rigorous review process for the procurement of embryos and gametes for stem cell research. In each case, procurement should follow generally accepted principles of research ethics, including those related to donor consent, relevant laws, policies, and regulations in the jurisdiction, as well as the principles laid down in the Guidelines.

- Tier 1: The procurement and use of banked and historical human cell lines is permissible if the materials have been deposited according to contemporaneous ethical and regulatory standards, and are distributed consistent with the original consent given for their use, along with additional provisions spelled out in the Guidelines. Notably, the latter include that Tier 1 cell lines should not be used for reproductive purposes, e.g. to create embryos from *in vitro*-derived gametes.
- Tier 2: The procurement of fresh human somatic cells and tissues for the purposes of stem cell research should be reviewed by existing review and oversight committees, bolstered by relevant stem cell expertise.
- Tier 3: The procurement of human gametes and embryos that are destined for use in human embryo research and stem cell research must be reviewed through the specialized oversight process as outlined in the Guidelines. This should include monitoring of the practices of donor

recruitment to ensure that the decision of women to donate their oocytes (or embryos) is free of undue inducement and exploitation.

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.

V. 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.

(i) 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.
- Encourage health systems and payers to establish a process for evaluating the health benefits and economic value of stem cell-based interventions.

(ii) 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.

- 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 U.S. FDA, the EMA, and Australia's TGA.
- 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.
- 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.
- 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.

VI. 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 five 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.

VII. REFERENCES

Clark, A., Brivanolou, A., Fu, J., Kato, K., Mathews, D., Niakan, K., Rivron, N., Saitou, M., Surani, A., Tang, F., and Rossant, J. (2021). Human embryo research, stem cell-derived embryo models and in vitro gametogenesis: considerations leading to the revised ISSCR guidelines. Stem Cell Reports 10.1016/j.stemcr.2021.05.008.

Daley, G.Q., Ahrlund Richter, L., Auerbach, J.M., Benvenisty, N., Charo, R.A., Chen, G., Deng, H.K., Goldstein, L.S., Hudson, K.L., Hyun, I., et al. (2007). Ethics. The ISSCR guidelines for human embryonic stem cell research. Science 315, 603–604. 10.1126/science.1139337.

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., et al. (2016). Setting Global Standards for Stem Cell Research and Clinical Translation. Stem Cell Reports 6, 787-797. 10.1016/j.stemcr.2016.05.001.

Deglincerti, 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 533,251-4. 10.1038/nature17948.

Doudna, J.A. (2020). The promise and challenge of therapeutic genome editing. Nature, 578, 229-236. 10.1038/s41586-020-1978-5.

Greenfield, A., Braude, P., Flinter, F., Lovell-Badge, R., Ogilvie, C., and Perry, A. (2017). Assisted reproductive technologies to prevent human mitochondrial disease transmission. *Nature biotechnology*, *35*(11), 1059–1068. 10.1038/nbt.3997.

Hyun, I., Bredenoord, A. L., Briscoe, J., Klipstein, S., and Tan, T. (2021). Human embryo research beyond the primitive streak. *Science*, *371*, 998–1000. 10.1126/science.abf3751.

Hyun, I., Clayton, E.W. Cong, Y., Fujita, M., Goldman, S.A., Hill, L.R., 10 Monserrat, N., Nakauchi, H., Pedersen, R.A. Rooke, H.M. et al. (2021). ISSCR Guidelines for the Transfer of Human Pluripotent Stem Cells and Their Direct Derivatives into Animal Hosts. Stem Cell Reports 10.1016/j.stemcr.2021.05.005.

Hyun, I., Lindvall, O., Ahrlund-Richter, L., Cattaneo, E., Cavazzana-Calvo, M., Cossu, G., De Luca, M., Fox, I.J., Gerstle, C., Goldstein, R.A., et al. (2008). New ISSCR guidelines underscore major principles for responsible translational stem cell research. Cell Stem Cell 3, 607-9. 10.1016/j.stem.2008.11.009.

Isasi, R., Andrews, P. W., Baltz, J. M., Bredenoord, A. L., Burton, P., Chiu, I. M., Hull, S. C., Jung, J. W., Kurtz, A., et al. (2014). Identifiability and privacy in pluripotent stem cell research. *Cell stem cell*, *14*(4), 427–430. 10.1016/j.stem.2014.03.014.

Isasi, R., Namorado, J., Mah, N., Bultjer, N., and Kurtz, A. (2019). A pathway for attesting ethical provenance of cell lines: Lessons from the European human pluripotent stem cell registry (hPSC^{reg}). *Stem cell research*, *40*, 101539. 10.1016/j.scr.2019.101539.

Knoppers, B. M., Isasi, R., Benvenisty, N., Kim, O. J., Lomax, G., Morris, C., Murray, T. H., Lee, E. H., Perry, M., Richardson, G., et al. (2011). Publishing SNP genotypes of human embryonic stem cell lines: policy statement of the International Stem Cell Forum Ethics Working Party. *Stem cell reviews and reports*, *7*(3), 482–484. 10.1007/s12015-010-9226-2.

Ma, H., Zhai, J., Wan, H., Jiang, X., Wang, X., Wang, L., Xiang, Y., He, X., Zhao, Z. A., Zhao, B., Zheng, P., Li, L., and Wang, H. (2019). In vitro culture of cynomolgus monkey embryos beyond early gastrulation. *Science 366*,10.1126/science.aax7890.

Matthews, K.R.W., Iltis, A.S., Marquez, N.G., Wagner, D.S., Robert, J.S., de Melo-Martín, I., Bigg, M., Franklin, S., Holm, S., Metzler, I., et al. (2021). Rethinking Human Embryo Research Policies. Hastings Cent Rep. 2021 Jan;51(1):47-51. 10.1002/hast.1215.

McCully S. (2021). The time has come to extend the 14-day limit. *Journal of medical ethics*, medethics-2020-106406. Advance online publication. https://doi.org/10.1136/medethics-2020-106406.

National Academy of Sciences 2020. Heritable Human Genome Editing. Washington,DC: The National Academies Press. https://doi.org/10.17226/25665.

National Academies of Sciences, Engineering, and Medicine. (2021). The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance. Washington, DC: The National Academies Press. https://doi.org/10.17226/26078.

Niu, Y., Sun, N., Li, C., Lei, Y., Huang, Z., Wu, J., Si, C., Dai, X., Liu, C., Wei, J.,et al. (2019). Dissecting primate early post-implantation development using long-term in vitro embryo culture. Science 366. 10.1126/science.aaw5754.

Shahbazi, M. N., Jedrusik, A., Vuoristo, S., Recher, G., Hupalowska, A., Bolton, V., Fogarty, N., Campbell, A., Devito, L., Ilic, D., et al. (2016). Self-organization of the human embryo in the absence of maternal tissues. *Nature cell biology*, *18*, 700–708. 10.1038/ncb3347.

Tan, T., Wu, J., Si, C., Dai, S., Zhang, Y., Sun, N., Zhang, E., Shao, H., Si, W., Yang, P.,et al. (2021). Chimeric contribution of human extended pluripotent stem cells to monkey embryos ex vivo. *Cell*, *184*, 2020–2032.e14. 10.1016/j.cell.2021.03.020

Williams, K., and Johnson, M. H. (2020). Adapting the 14-day rule for embryo research to encompass evolving technologies. *Reproductive biomedicine & society online*, *10*, 1–9. 10.1016/j.rbms.2019.12.002

TABLE 1: Categories of Research

CATEGORY 1	CATEGORY 2	CATEGORY 3
1A – Exempt from review by a specialized oversight process - Most *in vitro* pluripotent stem cell research - Most *in vitro* organoid research - Transfer of human stem cells into postnatal animal hosts	**2 – Reviewed by a specialized oversight process** - Procurement of embryos, or gametes for the creation of embryos, for *in vitro* research - Derivation of cell lines from human embryos - Genetic alteration of embryos or gametes - *In vitro* culture of human embryos for research	**3A – Not allowed: currently unsafe** - Germline genome editing for reproductive purposes - Transferring mtDNA-modified (not including MRT) embryos into a uterus - Using gametes differentiated from human stem cells for reproduction

1B – Reportable, but not typically reviewed by a specialized oversight process - Non-integrated stem cell-based embryo models - *In vitro* culture of chimeric embryos (human cells into non-human embryos) - *In vitro* gametogenesis without fertilization or generation of embryos	- Human cells transplanted into nonhuman embryos that are gestated in a non-human uterus - Integrated stem cell-based embryo models - Transferring human embryos following MRT into a human uterus	**3B – Not allowed: lacks compelling scientific rationale and/or is ethically concerning** - Gestating integrated human stem cell-based embryo models - Human reproductive cloning - Breeding human-animal chimeras where there may be human germ cells. - Transferring human-animal chimeric embryo(s) to a human or non-human primate uterus - Transferring human embryo(s), irrespective of origins, to an animal uterus

Legend: A brief summary of the categories of research from the 2021 ISSCR Guidelines for Stem Cell Research and Clinical Translation. For more detailed guidance, please see ISSCR.org/guidelines.

Table 2: THE PROCESS

The ISSCR Board established the Guidelines Revision Task Force, comprising 45 members (the authors of this article), in June 2019. This was carried out in consultation with the Chair, who had been identified earlier, and involved discussions with other key individuals to help ensure breadth and balance. It was felt important to ensure that the new Guidelines be developed by drawing on a wide range of perspectives, discplines, and backgrounds, and that it was not just informed by science, but by ethical, legal, regulatory, clinical, and commercial viewpoints.

Overview of structure

A Steering Committee comprising ten members was established, each with substantial experience in aspects of stem cell research and in formulating guidelines. The Committee included the Chair of the task force responsible for the previous revision of the ISSCR Guidelines in 2016. The Steering Committee oversaw the process via frequent online meetings and one in-person meeting in San Francisco in February 2020. The latter was an important occasion to establish the topics that would provide the focus of many of the revisions as well as providing a direction of travel for some of these.

The Task Force was also supported throughout by members of the ISSCR Policy and Outreach Teams, notably by Eric Anthony, Jack Mosher, and Glori Rosenson, who deserve much of the credit for the revised Guidelines.

The task force was divided into four Working Groups, each chaired by two Steering Committee members, with globally diverse expertise, and focused in four key areas:

(i) Genome editing and MRT

(ii) Embryos, embryo models and gametogenesis research

(iii) Organoid and chimera research

(iv) Regulatory, pricing, and access issues

The Working Groups and Steering Committee met often over the course of 15 months to draft and revise the Guidelines,

An early draft of the revised Guidelines was reviewed in May 2020 by the ISSCR Ethics, Public Policy, Clinical Translation, and Industry committees, and then by the ISSCR Board in June 2020. This led to a number of revisions and updates. The next draft was subject to extensive and international external peer review during September and October, 2020, which resulted in additional modifications. Based on this version, the main revisions being made in the Guidelines were then presented to ISSCR members in four separate briefings during November 2020. Further revisions and updates were then incorporated, before a more complete draft was given to the ISSCR Board, gaining their approval in December 2020. As the final version was being prepared, between then and now, some additional changes and updates were made, but in each case the wording was assessed by both the relevant Working Group and the Steering Committee.

Legend: An overview of the process undertaken to develop and review the 2021 Guidelines update.

Table 3: 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, in vitro human embryo culture, derivation of new embryo-derived cells or lines, integrated stem cell-based embryo models, 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, as appropriate, through a specialized oversight process capable of evaluating the unique aspects of the science and the associated ethical issues.
2.1.2	The specialized scientific and ethics oversight process must include an assessment of the scientific rationale and merit of research proposals, the relevant expertise of the researchers, and the ethical permissibility and justification for the research as discussed below.

2.1.3	The committee or body conducting the specialized scientific and ethics oversight process is responsible for (a) advising researchers on the categorization of research (see Recommendation 2.1.5), (b) determining whether a research proposal constitutes permissible or non-permissible research, (c) monitoring and periodically reviewing ongoing research, and (d) overseeing the provenance of the human pluripotent stem cell lines used in Category 2 Research (see section 2.1.5.2).
2.1.4	The specialized scientific and ethics oversight process should be conducted by qualified scientists, ethicists, legal and regulatory experts, and community members who are not directly engaged in the research under consideration. For additional information please see the explanation in Section 2.1.4 of the ISSCR Guidelines.
2.2	To ensure that human embryo and related stem cell research is proceeding with due consideration, to ensure consistency of research practices among scientists globally, and to specify the types of scientific projects that should be subject to review, the research review and oversight process should use the three categories described in this section.
2.2.1.1	Research involving the transfer of human stem cells or their direct neural and/or glial derivatives into the central nervous systems of postnatal animal hosts requires review by institutional animal research oversight committees supplemented by reviewer expertise in stem cell or developmental biology. (ISSCR Guidelines, 2006; Academy of Medical Sciences, 2011). Such oversight should weigh the potential benefits of the research and should utilize available baseline non-human animal data grounded in rigorous scientific knowledge or reasonable inferences and involve a diligent application of animal welfare principles.
2.2.2.1	Given advancements in human embryo culture, and the potential for such research to yield beneficial knowledge that promotes human health and well-being, the ISSCR calls for national academies of science, academic societies, funders, and regulators to lead public conversations touching on the scientific significance as well as the societal and ethical issues raised by allowing such research. Should broad public support be achieved within a jurisdiction, and if local policies and regulations permit, a specialized scientific and ethical oversight process could weigh whether the scientific objectives necessitate and justify the time in culture beyond 14 days, ensuring that only a minimal number of embryos are used to achieve the research objectives.
2.2.2.2	Chimeric embryo and in utero research described in 'Category 2, i' (see above) should proceed for the minimum time necessary to achieve the scientific aim. This research must proceed incrementally, stopping at well-defined timepoints to assess the degree and scope of chimerism during development before proceeding to full gestation, if full gestation is among the well-justified goals of the research. To avoid unpredictable and widespread chimerism, researchers should endeavor to use targeted chimerism strategies to limit chimerism to a particular organ system or region of the gestating chimeric animal.
2.2.2.3	Further research should be undertaken to refine and assess the safety and efficacy of Mitochondrial Replacement Techniques (MRT), including minimizing a) the risk of mitochondrial carryover and b) disruptions to the interaction between mitochondrial and nuclear genomes. In addition, further research on polar body transfer techniques and the use of mitophagy or genome editing is needed to reduce or eliminate pathogenic

	mitochondrial DNA. Such research should be subject to review by a specialized oversight process as Category 2 Research (Section 2.1.5.2).
2.2.3.1	Until there is further scientific clarity regarding how to achieve desired genetic alterations, additional evidence for safety, and wider discussion and consensus on ethics (i.e., whether it should be done and, if so, under which circumstances), any attempt to edit the mitochondrial genome or modify the nuclear genome of human embryos for the purpose of human reproduction is premature and should not be permitted at this time (see Section 2.2.3A, Category 3A, a).
2.3.1	The review process for the procurement of human cells and tissues should be predicated on the source of the material and its intended use as described in the three tiers: 1) banked and historical cell lines; 2) fresh human somatic cells and tissues; and 3) gametes and embryos.
2.3.2.1	Embryos, fetal tissue, and other cells and tissues should be used in research only if voluntary informed consent was obtained from the donors before the research commences. The informed consent process should be robust and document the prospect of therapeutic and commercial applications as well as the potential research uses, such as the creation of hESCs, iPSCs, other immortalized cell lines, embryos, and gametes. In the case of fetal tissue, consent from the woman donating the tissue is sufficient. In the case of embryos made with donor gametes, this consent should be obtained from the gamete donors and the party(ies) with authorization to donate the embryo.
2.3.2.2	Informed consent for research use must be distinct from informed consent for clinical treatment.
2.3.2.3	Review of procurement protocols must ensure that cell and tissue donors are adequately informed about the specific aspects of their voluntary research participation.
2.3.2.4	Researchers should develop a policy that states whether and how incidental findings will be provided to cell and tissue donors. This policy must be explained during the informed consent process. Cell and tissue donors should be able to choose whether they wish to receive incidental findings, if any. Reporting findings with relevance to public health may be required by law in certain jurisdictions.
2.3.2.5	Researchers are encouraged to discuss the potential for genomic sequencing to connect de-identified cells and tissues to donors and their relatives during the informed consent process for the donation.
2.3.3.1	Research oversight committees must authorize all proposals to reimburse for out-of-pocket expenses to donors of embryos, sperm, or somatic cells.
2.3.3.2	For the 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.
2.4.1	Proposals for derivations of new hESC lines should be scientifically justified and executed by scientists with appropriate expertise. A clear, detailed outline for banking new lines should be incorporated into derivation proposals. Whenever feasible, the distribution of new hESC lines to the research community is strongly encouraged following derivation and first publication.

2.4.2	National and international repositories should accept deposits of newly derived stem cell lines to preserve them, maintain them to a high standard, and ensure their authenticity. Repositories are encouraged to distribute them internationally to enable their dissemination. Researchers are encouraged to deposit data on stem cell lines into registries.
2.4.3	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 material transfer agreements and data demonstrating the identity of the cell line and uses allowed under the original informed consent. If a cell line has the potential to be used clinically, researchers are encouraged to provide information on the materials used for derivation and expansion.
2.4.4	Institutions engaged in human stem cell research performed with public funding are encouraged to develop procedures whereby researchers are granted access to research materials for scientifically and ethically appropriate purposes, as determined under these guidelines and applicable laws.
2.5.1	These guidelines should be upheld and enforced through standards of academic, professional, and institutional self-regulation.
3.1.1	Stem cells, cells, and tissues that are substantially manipulated or used in a non-homologous manner must be proven safe and effective for the intended use before being marketed to patients or incorporated into standard clinical care.
3.2.1.1	Donors of cells for allogeneic use should give written and legally valid informed consent that covers, where applicable, terms for potential research and therapeutic uses, disclosure of incidental findings, potential for commercial application, and issues specific to the type of intervention under development.
3.2.1.2	Donors for allogeneic stem cell-based interventions should be screened and tested for infectious diseases and other risk factors, in compliance with applicable regulatory guidelines (see Recommendation 2.4.3).
3.2.2.1	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. Manufacturing should be performed under GMP conditions when possible or mandated by regulation. However, in early-stage clinical trials it is understood that GMPs may be introduced in a phase appropriate manner in some regions.
3.2.2.2	The oversight and review of cell processing and manufacturing protocols should be rigorous, and consider the manipulation of the cells, their source and intended use, the nature of the clinical trial, and the research subjects who will be exposed to them.
3.2.2.3	Human or chemically defined components should be used in the culture or preservation of cells whenever possible.
3.2.2.4	All reagents used in manufacturing stem cell-derived therapeutics should be of the highest quality available.
3.2.2.5	Criteria for in process and release specifications should be developed during the regulatory review process. Culture-acquired genetic abnormalities may be a significant risk and should be part of in process and/or final product testing for stem cell products that have undergone extensive expansion in vitro.

3.2.2.6	Criteria for release of cells should include the assessment of off-target cells, using the most sensitive assays possible.
3.3.1.1	Preclinical research into stem cell-based interventions involving animals 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.
3.3.1.2	Early phase human studies should be preceded by a rigorous demonstration of safety and efficacy in preclinical studies. These preclinical studies can include in vitro and in vivo modeling.
3.3.1.3	All preclinical studies testing safety and efficacy should be designed in ways that support precise, accurate, and unbiased measures of potential clinical utility. In particular, studies designed to inform trial initiation should have high internal validity; they should be as representative as possible of clinical scenarios they are intended to model, and they should be replicated.
3.3.1.4	Preclinical studies should assess both male and female animals in safety and efficacy testing unless there is a scientifically valid reason not to do so.
3.3.2.1	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 animal models.
3.3.2.2	Risks for tumorigenicity must be rigorously assessed for any stem cell-based product, especially if cells are extensively manipulated in culture, genetically modified, or when derived from a pluripotent source.
3.3.2.3	For all stem cell-based products, whether injected locally or systemically, researchers should perform detailed and sensitive biodistribution studies of cells.
3.3.2.4	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.
3.3.2.5	Researchers should adopt practices to address long-term risks in preclinical studies.
3.3.2.6	Researchers should comprehensively investigate the type, extent and genomic distribution of introduced genetic alterations as well as their potential adverse effects on the genome and the biological properties of the treated cells at short and long-term time points.
3.3.2.7	Researchers, sponsors, and regulators should take advantage of the potential for using stem cell-based systems to enhance the predictive value of preclinical toxicology studies.
3.3.3.1	Trials should generally be preceded by compelling preclinical evidence of clinical utility 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, or if it is not feasible to establish appropriate or predictive animal models.
3.3.3.2	Appropriate animal models should be selected which allow the assessment of efficacy and safety of the stem cell-based intervention. Safety testing should include assessment of the delivery procedure or surgical technique used for implantation of the cells.
3.3.4.1	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.

3.4.1.1	All research involving clinical applications of stem cell-based interventions must be subject to prospective review, approval, and ongoing monitoring by independent human subjects research review committees.
3.4.1.2	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.
3.4.2.1	Risks should be identified and minimized, unknown risks acknowledged, and potential benefits to subjects and scientific understanding estimated. Sponsors should be able to justify research with human subjects in terms of likely risk and benefit based on evidence from preclinical studies and the published literature.
3.4.2.2	Initiation of clinical trials should be supported by a systematic appraisal of evidence supporting the intervention and the current unmet need for treatment of the disease or disorder.
3.4.2.3	Stem cell-based interventions must be aimed toward being clinically competitive with existing therapies or meeting a unique therapeutic demand. Being clinically competitive necessitates having reasonable evidence that existing treatments are less than optimal or pose burdens that may be overcome should the stem cell-based intervention prove to be safe and effective.
3.4.2.4	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 scientific justification. Unless scientifically inappropriate, trials should strive to proportionally include women, as well as men, and members of all ethnic groups.
3.4.2.5	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 are identified or alternative treatments emerge during the research.
3.4.2.6	When human research participants lack the capacity to provide valid informed consent, when no other reasonably effective options exist, and the risks from study procedures should be limited to no greater than a minor increase over the minimal risk unless the risks associated with the intervention are exceeded by the prospect of therapeutic benefit. A legally authorized representative or substitute decision-maker should help make decisions that are in the patient's interest.
3.4.2.7	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.
3.4.2.8	Research teams must protect the privacy of human subjects.
3.4.2.9	Patient-sponsored and pay-to-participate trials pose challenges for ensuring scientific merit, integrity, and priority as well as fair selection of study participants. Accordingly, charging individuals to participate in clinical trials should only be permitted when such

	studies are compliant with applicable national regulations and are approved and supervised by a rigorous independent review body, such as an institutional review board.
3.4.3.1	All trials should be prospectively registered in public databases.
3.4.3.2	Investigators should report adverse events, including their severity and potential causal relationship with the experimental intervention.
3.4.3.3	Researchers should promptly publish results regardless of whether they are positive, negative, or inconclusive. Studies should be published in full and according to international reporting guidelines, including registration in the public databases.
3.4.4.1	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.
3.4.4.2	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.
3.4.4.3	Researchers should take measures to maximize the scientific value of early phase trials.
3.4.5.1	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.
3.4.5.2	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 historical controls, placebo, or sham comparators, assuming early experience has demonstrated the feasibility and safety of the particular intervention.
3.4.6.1	A 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.
3.4.6.2	Given the potential for transplanted cellular products to persist indefinitely and depending on the nature of the experimental stem cell-based intervention, subjects should be advised to undergo long-term health monitoring. Long-term follow-up is mandated in some countries, often for the use of gene therapies or xenotransplants. Additional safeguards for ongoing research subject privacy should be provided. Subject withdrawal from the research should be made in an orderly fashion to promote physical and psychological welfare.
3.4.6.3	To maximize the opportunities for scientific advance, research subjects or surviving next of kin 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 at some point in the trial. Requests for an autopsy must consider cultural and familial sensitivities and be conducted in a respectful and compassionate manner. 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.

3.4.7.1	The clinical use of genetically altered (including genome-edited) somatic stem cells should be reserved for the treatment or correction of severe disease and disability. Due to the inherent risks, these products should comply with established policies and regulations for genome editing and cell-based products.
3.4.8.1	Mitochondrial Replacement Techniques (MRT) should be offered only in the context of clinical investigation that is subject to strict regulatory oversight, limited to patients at high risk of transmitting serious mitochondrial DNA-based diseases to their offspring, when no other treatments are acceptable, and where long-term follow-up is feasible. International data sharing arising from initial uses is essential to help inform the field and ensure its appropriate use.
3.4.8.2	There are inadequate clinical and preclinical data to justify the use of MRT to treat unexplained infertility associated with poor oocyte/embryo quality in women; therefore, it is recommended that this not be an intervention at this time..
3.4.8.3.1	Substantial preclinical research is needed to minimize the potential harm associated with clinical applications involving germline genome editing; therefore, any attempt to modify the nuclear genome of human embryos for the purpose of reproduction is premature and should not be permitted at this time (see Section 2.1.3.3, Category 3A, a).
3.4.8.3.2	If the technical and safety challenges associated with human germline genome editing are resolved (see Recommendations 2.1.4 and 3.4.8.3.1), any applications for the initial clinical use of human germline genome editing should be evaluated on a case-by-case basis. This evaluation needs to consider not just the scientific methods, but also the societal and ethical issues associated with the proposed use.
3.4.8.3.3	A comprehensive regulatory and ethical framework for overseeing germline genome editing must be established before any first-in-human clinical applications are considered. This framework should build on the existing regulatory frameworks for new biotechnologies, the practice of medicine, and the principles outlined in these guidelines (see Section 3.3 and 3.4).
3.4.8.3.4	Regulators, research funders, and academic and medical societies should seek to prevent the premature or unethical clinical uses of germline genome editing unless and until the safety, ethical, and societal issues associated with the clinical use of germline genome editing are resolved.
3.4.9.1	Clinical research involving in utero stem cell-based interventions or genome editing involves risks to both the pregnant woman and the future child, and should be undertaken only when it offers the prospect of a benefit greater than that of post-natal interventions, does not pose excessive risk to the pregnant woman, and where there is institutional capacity for autopsy (in the case of miscarriage or stillbirth) or follow-up (in the case of live birth).
3.5.1	The clinical use of unproven stem cell-based interventions should be limited to well-regulated clinical trials and medical innovations compliant with these guidelines (Recommendation 3.5.2) and local laws, policies, and regulations. Government authorities and professional organizations should establish and strictly enforce policies and regulations governing the commercial use of stem cell based medical interventions.

3.5.2	Given the many uncertainties surrounding medical innovations involving stem cells and their direct derivatives, this pathway is rarely ethically and scientifically justifiable and should be limited to a very small number of patients and restricted to a) the off-label use of authorized therapies (see Recommendation 3.5.3), b) unproven interventions provided through expanded access pathways (see Recommendation 3.5.4), or c) minimally manipulated stem cell based interventions for homologous uses. Such interventions should only be provided to patients according to the highly restrictive provisions outlined in this section and the other referenced recommendations.
3.5.3	Off-label uses of stem cell-based interventions should be employed with particular care, given uncertainties often associated with off-label uses generally and associated with stem cell-based interventions specifically.
3.5.4	Pre-approval access to experimental stem cell-based interventions should be limited to well-regulated programs that require prior authorization from national regulators.
3.6.1.1	The introduction of novel products into routine clinical use should be dependent on the demonstration of substantial evidence of effectiveness in appropriately powered, well-controlled clinical trials, with statistically significant findings.
3.6.1.2	When evaluating new interventions for rare diseases or life-threatening medical conditions, regulators should consider the acceptable balance of risk and clinical benefit appropriate to the medical condition and patient population for which new treatments are designed. All approval pathways should require substantial evidence of safety and effectiveness before products are marketed to patients.
3.6.1.3	In jurisdictions with conditional approval mechanisms, regulators must ensure there is a robust post-market surveillance system whereby regulators have the capacity and power to remove products from the market as appropriate.
3.6.1.4	In jurisdictions with existing approval pathways for orphan or rare diseases, those pathways should be used to facilitate the development of stem cell-based interventions.
3.6.1.5	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.
3.6.1.6	Registries of specific patient populations should be used to provide valuable data on the natural history and progression of diseases that can support the development of meaningful endpoints, biomarkers, and outcomes measures to facilitate the development of new products. Furthermore, patient registries are useful tools for monitoring adverse events after regulators have approved a product for routine clinical use. However, registries should not be substituted for well-regulated randomized controlled clinical trials designed to evaluate the safety and efficacy of complex products like stem cell and gene-based interventions.
3.6.1.7	Provision and use of equipment and commercial kits for cell and gene-based interventions in humans should be limited to settings with an appropriate level of regulatory oversight to ensure their safe and responsible use.
3.6.2.1	Stem cell-based interventions should be developed to deliver health and economic value to patients, payers, and healthcare systems.

3.6.2.2	Payers, and healthcare systems should work with developers of stem cell interventions, patients, and regulators to establish processes to evaluate their health and economic value, including conditional pathways.
3.6.2.3	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, current, 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.
4.3	The provision of information to patients considering stem cell-based interventions must be consistent with the primacy of patient welfare, scientific and ethical integrity.
5.1	Researchers, industry, and regulators should work towards developing and implementing standards on design, conduct, interpretation, preclinical safety testing, and reporting of research in stem cell science and medicine.
5.2	The ISSCR guidelines should be periodically revised to accommodate scientific advances, new challenges, and evolving social priorities.

Table 3 Legend: A compilation of all the recommendations from the ISSCR Guidelines for Stem Cell Research and Clinical Translation

Table 4: Summary of Significant Changes in the 2021 ISSCR Guidelines for Stem Cell Researhc and Clinical Translation.

REVIEW PROCESS

1. Renames EMRO review process to a "specialized oversight process capable of evaluating the unique aspects of the science and the associated ethics issues."
2. Clarifies that the review process can occur at the institutional or national level.

CATEGORIES OF RESEARCH

1. Divides Category 1 and 3 into two subcategories each. The changes to the research categories are noted below.
    - 1A – Exempt from specialized oversight process (review by existing oversight review processes).
        - Most *in vitro* pluripotent stem cell research [unchanged, previously Category 1]
        - Fetal tissue [new for clarity]
        - Research that involves transplanting human cells into non-embryo animals [new for clarity]
        - Organoids [new]
    - 1B – Reportable, but not typically subject to further or ongoing review.
        - *In vitro* culture of chimeric embryos (with human cells)
        - Non-integrated stem cell-based embryo models [formerly category 2]
        - *In vitro* gametogenesis without fertilization or generation of embryos [new]
        - In vitro chimeric embryo research [new]
    - 2 – Review through specialized oversight process.
        - Procurement of human gametes, embryos, etc. [unchanged]
        - Derivation of cell lines from human embryos [unchanged]
        - In vitro genetic alteration of human embryos or gametes [unchanged]
        - Integrated stem cell-based human embryo models for the minimum time necessary to achieve scientific objective [previously limited to 14 days or formation of primitive streak]
        - Transferring human embryos following MRT into a human uterus [new]
        - Transferring chimeric embryos into a non-human uterus, excluding transfer into greater and lesser apes, which is prohibited [new]
    - 3A – Research activities currently not permitted because it is currently unsafe or raises unresolved ethical issues.
        - Germline genome editing of the nuclear DNA of a human embryo followed by transfer to a uterus [unchanged, previously Category 3]
        - Germline genome editing of the mitochondrial DNA of a human embryo followed by transfer to a uterus [new for clarity]
        - Using gametes differentiated from human stem cells for reproduction [new]
    - 3B – Prohibited research activities because of a broad international consensus that such research lacks a compelling scientific rationale or is widely considered to be unethical.
        - Transferring stem cell-based human embryo models to a uterus [unchanged, previously Category 3]
        - Transferring an IVG-derived human embryo into the uterus of an animal host [new]
        - Human reproductive cloning [unchanged, previously Category 3]

- Breeding human-animal chimeras that may have or have the potential to form human gametes [unchanged, previously Category 3]
- Transferring human-animal chimeric embryos to a human or ape uterus [new]

- New recommendation on 14-day rule: Given advancements in human embryo culture, and the potential for such research to yield beneficial knowledge that promotes human health and well-being, the ISSCR calls for national academies of science, academic societies, funders, and regulators to lead public conversations touching on the scientific significance as well as the societal and ethical issues raised by allowing such research. Should broad public support be achieved within a jurisdiction, and if local policies and regulations permit, a specialized scientific and ethical oversight process could weigh whether the scientific objectives necessitate and justify the time in culture beyond 14 days, ensuring that only a minimal number of embryos are used to achieve the research objectives.

PROCUREMENT OF CELLS AND TISSUES / DERIVATION OF STEM CELL LINES

1. New three-tiered review system to streamline the review process for the procurement of banked and historical cell lines, while maintaining the rigorous review process for the procurement of embryos and gametes for stem cell research.
2. Updated recommendations on the derivation and banking of new lines to facilitate the development of stem cell-based products.

CLINICAL TRANSLATION

1. Adopts international standards for defining stem cell-based products as drugs or ATMPs if such products have been substantially manipulated or are provided for non-homologous uses. This standard broadly aligns the Guidelines with the regulations from U.S. FDA, EMA, and Australia's TGA.
2. Includes a new recommendation on sex as a biological variable.
3. Strengthens 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.
4. Includes a new recommendation to forcefully caution against the premature commercialization of unproven stem cell-based interventions.
5. Narrows the types of stem cell-based products eligible for the medical innovation pathway that is aligned with international regulatory standards, including the U.S. FDA.
6. Includes 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.
7. Supports the use of accelerated approval pathways based on surrogate or intermediate endpoints.
8. Encourages robust post-market surveillance systems in jurisdictions with conditional approval pathways.
9. Encourages health systems and payers to establish a process for evaluating the health and economic value of stem cell-based interventions.

GENOME EDITING

1. New recommendation on somatic genome editing that reserves the clinical use of genetically altered (including genome-edited) somatic stem cells for the treatment or correction of severe disease and disability.
2. New recommendations on MRT that encourage more research to refine and assess of the safety and efficacy of MRT.
3. Recommends limiting the clinical use of MRT to those at high risk of transmitting serious mitochondrial DNA-based diseases to their offspring and when no other treatments are acceptable.
4. Recommends that there is no use of MRT for unexplained infertility associated with poor oocyte/embryo quality in women due to inadequate pre-clinical data.
5. New Recommendations on Heritable Germline Genome Editing.
    - Prohibits clinical applications involving germline genome editing and encourages preclinical research to minimize the potential harm associated with such applications.
    - 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.
    - Encourages the development of a comprehensive regulatory and ethical framework for overseeing germline genome editing that builds on the existing regulatory frameworks for new biotechnologies, the practice of medicine, and the principles in the ISSCR Guidelines.
6. New guidance on *in utero* genome and stem cell-based interventions: 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 only when it offers the prospect of a benefit greater than that of post-natal interventions, does not pose excessive risk to the pregnant woman, and where there is institutional capacity for autopsy (in the case of miscarriage or stillbirth) or follow-up (in the case of live birth).

Legend: A summary of the significant changes between the 2016 and 2021 ISSCR Guidelines for Stem Cell Research and Clinical Translation.

CONFLICTS OF INTEREST:

Robin Lovell-Badge has no financial conflicts to declare. Lovell-badge 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.

Roger Barker receives funding from UK NIHR, MRC, Wellcome, Cure Parkinson's Trust and EU. I have received funding from Parkinson's UK, CHDI, Rosetrees Trust and Evelyn Trust. I receive royalties from Wiley and Springer and also have an ongoing consultancy role for the following companies- Novo Nordisk; UCB; Aspen Neuroscience; BlueRock Therapeutics.

Ali H. Brivanlou is a co-founder of OvaNova Inc., as well as a co-founder of Rumi Scientific Inc.

R. Alta Charo is Professor Emerita, University of Wisconsin; David Hamburg Fellow, Nuclear Threat Initiative; and Lead Co-Chair, BioMADE. Charo 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 science, technology and innovation.

Amander Clark Board Member of the ISSCR, Scientific Advisory Board Member of the Tepper Foundation.

George Q. Daley holds patents relevant to stem cells and is a founder of and member of the scientific advisory board of 28/7 Therapeutics, Inc.

Steve Goldman is also a part-time employee and stock-holder of Sana Biotechnology, a cell therapy company; he holds relevant patents and his lab receives sponsored research support from Sana.

Andy Greenfield is a current or recent board member of the following: the National Academies International Commission on Heritable Human Genome Editing; the UK HFEA's Scientific & Clinical Advances Advisory Committee; and the UK Nuffield Council on Bioethics until 2020. Greenfield's core funding is from the Mammalian Genetics Unit at MRC Harwell (MC_U142684167).

Juergen Knoblich holds a patent on the cerebral organoid method and am co-founder and scientific advisory board member of a:head bio.

Debra JH Matthews is a member of the Maryland Stem Cell Research Commission and a paid Academic Collaborator of the National Academy of Medicine's Committee on Emerging Science, Technology, and Innovation in health and medicine.

Luigi Naldini is an inventor on patents on lentiviral vector technology and targeted genome editing filed by Telethon Foundation and/or San Raffaele Scientific Institute. LN is a founder and/or owns equity, and is a scientific advisory board member of Genenta Science, Magenta Therapeutics, Genespire, Tessera.

Roger Pederson is an advisor and has stock options in BIT BIO.

Janet Rossant is a Member Board of Directors, Notch Therapeutics; Member, Editorial Board, Stem Cell Reports; and Member, Editorial Board, Cell Stem Cell.

Nicolas Rivron is an inventor on two patents describing the blastoid technology (EP2986711 and EP21151455.9). Rivron has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program ERC-Co grant agreement No. 101002317.

Mitinori Saitou is affiliated with the following: Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan; Department of Anatomy and Cell Biology, Graduate School of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan; and Center for iPS Cell Research and Application (CiRA), Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Saitou is an inventor on patent applications relating to the induction of germ cells from PSCs filed by Kyoto University.

Jeremy Sugarman is a member of Merck KGaA's Bioethics Advisory Panel and Stem Cell Research Oversight Committee; a member of IQVIA's Ethics Advisory Panel; a member of Aspen Neurosciences Scientific Advisory Board; a member of a Merck Data Monitoring Committee; a consultant to Biogen; and a consultant to Portola Pharmaceuticals Inc.

Leigh Turner has no financial interests to declare. Turner is member of ISSCR's Ethics Committee and Membership Committee and was a member of one of the Working Groups involved in revising and updating ISSCR's guidance document.

The following authors declare no competing interests: Eric Anthony, Tania Bubela, Ellen Clayton, Yali Cong, Jianping Fu, Misao Fujita, Lori Hill, Insoo Hyun, Rosario Isasi, Jeffrey Kahn, Kazuto Kato, Jonathan Kimmelman, Nuria Montserrat, Megan Munsie, Jack Mosher, Hiromitsu Nakauchi, Kathy Niakan, Ubaka Ogbogu, Heather Rooke, Azim Surani, Fuchou Tang, Jun Takahashi, Patricia J Zettler,