Group 2 focused on the proposed revie categories and the t pes of research that should fall under each heading.

The 2016 guidelines had three categories of revie ; the ne guidelines divide t o of these categories, to provide clearer delineation of the different levels of revie .

2016 Categor 1: E empt from revie
- **New Categor 1A:** E empt from revie
- **New Categor 1B:** Reportable to an oversight process but normall e empt from revie

2016 Categor 2: Requires revie ; categor is unchanged although the areas of research under this heading have increased

2016 Categor 3: Prohibited research activities
- **New Categor 3A:** Research activities currentl not permitted
- **New Categor 3B:** Prohibited research activities

The rationale for these changes, as ell as the areas of research that ould fall into the different categories are described in more detail in the follo ing sections. It is important to note up front that the culture of human embr os or organi ed embr o-like structures be ond 14 da s, or formation of the primitive streak, hichever occurs, rst (herein referred to as the "14-da rule"), has been removed from categor 3, prohibited activities. This as the subject of man levels of discussion, debate, and consultation over man months. While recogni ing that human embr o culture be ond 14 da s is prohibited b la or regulation in man jurisdictions, the committee felt that this is an area here a blanket prohibition could inhibit important research directions. The scienti c, ethical, and regulator background to this recommendation is discussed further in later sections.

The decision to update the categories of scientific and ethical review

The decision of the committee to update the laborator science covered b the different categories re ects not onl the changing landscape of stem cell research but also the challenge in de ning the concept of "organislt2(h)s3.9(pten)13.1(r)20.92,l, .8('1.8(co2(a)1'r)-271t2.i00scn2o)149281, b55oc0.9(hT

Category 3A: Research activities currently not permitted. Research under this category should not be pursued at this time because the approaches are currently unsafe or raise unresolved ethical issues. Some examples include:

a. The use of human gametes differentiated from human stem cells for the purposes of fertilization and human reproduction.
b. Research in which human embryos that have undergone modification of their nuclear genome are transferred into or gestated in a human uterus.

Category 3B: Prohibited research activities. Research under this category should not be pursued because of broad international consensus that such experiments lack a compelling scientific rationale and are widely considered to be unethical. Such research includes:

a. Transfer of human stem cell-based embryo models to the uterus of either a human or animal host.
b. Research in which animal chimeras incorporating human cells with the potential to form human

use of the umbrella term “embr o model” or “stem cell-based embr o model” is encouraged, hile the use of the term “s nthetic embr o” or “arti cial embr o” or “embr - oids” should be avoided. Furthermore, the establishment of a terminolog precisel re ecting the degree of integration and the t pe of model is encouraged (e.g., t- t t t [[Zheng et al., 2019], t [Rivron et al., 2018a]).

Integrated versus non-integrated embryo models

Here, e propose a classi cation of human embr o models ith the aim of guiding the decisions of the scienti c and ethical oversight process. The - t t ill be models that mimic onl speci c aspects/tissues of human embr o development and often do not have an associated e tra-embr onic membranes. - t - t are reportable but not normall subject to further revie (categor 1B). In contrast, the t t hich contain the relevant embr onic and e tra-embr onic cell t pes and could potentiall achieve the comple it here the might realisticall manifest the abilit to undergo further integrated development if cultured for additional time t should be subjected to a full speciali ed revie (categor 2). Given that the stem cell-based embr o models are not considered equivalent to human embr os under most legislation (as described in detail above), the decision as made that the integrated embr o models should not be subject to the restrictions of the 14-da rule. In addition, for both ethical and safet reasons, transferring an human embr o model into the uterus of a living animal or human is prohibited (categor 3B).

Examples and potential applications

B recapitulating t earl human embr onic events, the use of human embr o models for scienti c discover opens ethical alternatives to addressing important biomedical problems. For e ample, in the ne t decade, - t t are likel to model speci c events that occur during the rst fe months of human embr o development, including gastrulation, bod a is formation, and somitogenesis, thus allo ing the investigation of numerous aspects of embr ogenesis-related pregnanc problems and geneticall inherited defects. Furthermore, the - t t are likel to help researchers to gain basic kno ledge of the speci c molecular and cellular events associated ith genome mutations associated ith developmental origins of disease. The should also guide drug discover and biomedical strategies aiming at managing genetic diseases or forming or regenerating comple organs for regenerative medicine. E amples of such models include human pluripotent stem cells gro n on micropatterned t o-dimensional surfaces ith con ned geometr (Warm ash et al., 2014), t (Moris et al., 2020; van den Brink et al., 2014), (Zheng et al., 2019), or (Haremaki et al., 2019).

Stem cell-derived t that mimic the blastoc st stage of development have been produced in the mouse (Kime et al., 2019; Li et al., 2019; Rivron et al., 2018b; So en et al., 2019) and ver recentl in the human (Liu et al., 2021; Yanagida et al., 2021;

including PGCLCs, oogonia- or oocyte-like cells, or

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