International Regulation of Neural Organoids and Chimeras

National Academies of Sciences, Engineering, and Medicine
Committee on Ethical, Legal, and Regulatory Issues Associated with Neural Chimeras and Organoids

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Agenda

- Introduction and Background
- US Framework
- International Regulatory Landscape

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- **Introduction and Background**
- **US Framework**
- **International Regulatory Landscape**

Legal Framework – Questions to Consider

Your charge includes:

- What regulatory mechanisms relating to organoid and chimeric animal research are currently in place? Are there gaps in the current regulatory framework?
- What regulatory mechanisms exist for similar research?
- What further regulatory mechanisms might be appropriate?

Legal Frameworks Across the Globe

- Generally do not expressly reference neural organoids or chimeras.
- Instead, existing parameters rely on standards from other laws and requirements, largely related to embryonic stem cell (ESC) research.
- Additional boundaries found in standards for animal research protections, safety and quality, product approval, and human subjects protection (for donors).

Considerations for a Regulatory Framework

- Specific informed consent for donated embryos.
- Permitted or prohibited research uses of biological material, including
  - Therapeutic purposes for embryonic studies, and
  - Reproductive purposes for embryonic studies.
- Exclusion of embryos created specifically for research.
- Import or export of cloned materials.
- Period when an embryo may be used for research purposes.
- Animal welfare.

Background – Definitions

- **Stem cell**: A cell that has the ability to divide for indefinite periods in culture and to give rise to specialized cells.
  - Totipotent stem cells are able to divide and differentiate into cells of the whole organism.
  - After approximately 4 days, the blastocyst's inner cell mass becomes pluripotent. This structure is the source of pluripotent cells.
  - Pluripotent stem cells (PSCs) form cells of all germ layers but not extraembryonic structures, such as the placenta. **Embryonic stem cells (ESCs)** are an example.
  - ESCs are derived from the inner cell mass of preimplantation embryos.
  - Induced pluripotent stem cells (iPSCs) derive from the epiblast layer of implanted embryos. Their pluripotency is a continuum, starting from completely pluripotent cells such as ESCs and iPSCs and ending on representatives with less potency—multi-, oligo- or unipotent cells.

Neural Organoids

- **Organoids**: Self-organizing three-dimensional structures, generated *in vitro* from stem cells (i.e., adult tissue-specific, iPSC, and embryonic stem cells) that resemble *in vivo* organs in terms of their structure and function.
- They offer great promise for understanding biology, development and disease, drug development, personalized medicine, organ transplantation and other applications.
  - Neural organoids have been used to study Alzheimer's, autism, schizophrenia, and more.
- Because they are created from stem cells, they are subject to limits on the use of stem cells, e.g., from the National Institutes of Health (NIH).

Neural Chimeras

- **Human-animal Chimeras**: Animals into which human cells have been introduced.
  - Neural chimeras range from a single human cell to whole replacement of animal brain (neuronal and non-neuronal cells).
  - They include animals in which human neural organoids are grafted.
  - Techniques include “blastocyst complementation,” in which human stem cells transferred into preimplantation animal embryos.

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Overview: US Regulatory System

Federal Laws apply to research:

- With federal funding, *e.g.* the Common Rule, *NIH Guidelines*
- Involving an FDA-regulated products and no intent to be used in support of a marketing application to the FDA, or
- That crosses limited bars, *e.g.,* for cloning.

State Laws may address:

- Activity within state or with state funding
  - Sources and materials, *e.g.*, embryos and stem cell lines
  - Protection of research subjects

US Funding: NIH and Stem Cells

- March 9, 2009: Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*
  - Authorized funding for human stem cell research, and
  - Prohibited the use of NIH funds for introducing human stem cells into early-stage embryos of non-human primates.

- July 7, 2009: National Institute of Health ("NIH") issued the *NIH Guidelines for Human Stem Cell Research*
  - Allow research with stem cells that are derived from embryos created by IVF for reproductive purposes that are no longer needed and donated by individuals who have given their informed consent, and
  - Prohibits the use of stem cells in research with blastocyst stage nonhuman primate embryos

US Funding: NIH and Chimeras

- **September 23, 2015:** NIH notice confirmed the NIH would no longer fund research "in which human pluripotent cells are introduced into non-human vertebrate animal pre-gastrulation stage embryos while the Agency considers a possible policy revision in this area."
  - Concern about growing human tissue and organs in animals by introducing human stem cells into early stage non-human vertebrate embryos.
  - Agency would not fund "any new or competing grant applications or contract proposals for research in which human pluripotent cells are introduced into non-human vertebrate animal pre-gastrulation stage embryos."
- **August 4, 2016:** NIH released a notice requesting public comment on proposed changes to the NIH Guidelines for Human Stem Cell Research.
  - Proposal included expand the *2009 Guidelines* prohibition on stem cell use in non-human primate embryos.

US Funding: NIH and Embryo Research

- 1996 -> present: **Dickey-Wicker Amendment** bars the Department of Health and Human Services ("HHS") from using federal funds for:
  - (1) the creation of a human embryo or embryos for research purposes; or
  - (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero . . ."
    - Human embryo is defined to include "any organism . . . that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."
- Research involving embryos is permitted so long as the above criteria are satisfied.

US Common Rule

- The Federal Common Rule (45 C.F.R. pt. 46, subpt. A) applies to “human subjects,” meaning a living individual about whom an investigator obtains:
  - Data or biospecimens through intervention or interaction with an individual
  - Identifiable private information or identifiable biospecimens (i.e., the identity of the subject is, or readily may be, ascertained by the investigator or is associated with the information)
- Embryos and hESC are not living individuals, so the Common Rule (45 CFR 46) does not apply:
  - But, Dickey-Wicker mandates that embryos in federally-funded research not be subjected to research risks greater than a fetus could be subjected to under former 45 C.F.R. 46.208(a)(2).

US Common Rule plus NIH

- Donors of embryo tissue for research are human subjects:
  - Informed Consent, and
  - IRB review for donation protocols.

- *NIH Guidelines for Human Stem Cell Research* (2009)*:*
  - Impose extensive requirements for donor consent
  - Include limits on sources, use, and transfer to animals.

US Oversight System: FDA

- No federal laws or regulations directly apply to the use of embryos in privately-funded research
  - FDA does not regulate bench research on embryos that does not involve reproductive or therapeutic application.
- FDA, through the Center for Biologics Evaluation and Research (CBER), does regulate:
  - Embryo research to the extent that the research involves development of a “biologic product” that would be applicable to the prevention, treatment or cure of diseases or injuries to humans. 42 U.S.C. § 262(i)(j) and 21 C.F.R. § 600.3.
  - Human cells, tissues, and cellular and tissue-based products (HCT/P)
    - an article “containing or consisting of human cells and tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.” 21 C.F.R. §1271.3.

State Law: Patchwork Quilt

California:	Research using human embryos generally **permitted**, including allowing for the creation of human embryos for research purposes.
Louisiana:	Specifically **prohibits** research on IVF embryos.
Massachusetts:	Research using human embryos generally **permitted**, but **prohibits** human reproductive cloning and creation of an embryo for research purposes.
South Dakota:	**Prohibits** research on embryos, regardless of source.

Sources:

California Health and Safety Code §§ 123440, 24185, 125300–125356.

La. Stat. Ann. § 14:87.2.

Mass. Gen. Laws ch. 111L §§ 3, 8.

S.D. Codified Laws §§ 34-14-16, 17, 20; 34-23A-17.

US Oversight: USDA

The US Animal Welfare Act is the primary Federal law in the United States that regulates the treatment of animals in research (also, exhibition, transport, and by dealers). Other laws, policies, and guidelines may include additional species coverage or specifications for animal care and use, but all refer to the Animal Welfare Act as the minimum acceptable standard. 7 U.S.C. § § 2131-2159.

- recognizes the capacity of animals to suffer or be distressed, which implies a state of mental suffering.
- requires research facilities to ensure that environments provided for non-human primates promote the “psychological well-being” of the animals.
- only applies to certain animal species and contains wide exemptions.

State legislation in animal welfare is limited in scope and inconsistent between states. Many state laws include language regarding the physical and psychological suffering of animals. For example:

- New York’s Elephant Protection Act prohibits the use of elephants in any type of entertainment act and acknowledges that ‘elephants are complex, highly intuitive and intelligent animals.’

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International Landscape of Organoid and Chimeric Animal Research

	Canada	United Kingdom	EU (Italy, Germany)	Japan	China
Current Research Activity	$4 million investment by Canada's Stem Cell Network in April of 2018, 24 projects involving stem cell research have been planned, involving 95 scientists across the country.	After scientists successfully cloned a sheep in Scotland back in 1996, Britain has been Europe's leader in stem cell research.	Within stem cell research, countries with restrictive policies, such as Germany and Italy, nevertheless achieved high citation impact, illustrating the complex relationship between policy and practice. Of note, both Italy and Germany permit the use of imported hES cell lines (although Germany does place restrictions on such importation).	iPSC is an innovation of Japan, now leading for quality commercialization of iPSC-derivatives, and also becoming the world first nation to conduct pretrial clinical studies. Recognizing their discovery and productive market, Japan government amended the Pharmaceutical and Medical Device Act (PMDA) in Nov 2013 opening door for regenerative medicine products. As the first government to support creation of animal embryos containing human cells and permit transplantation into surrogate animals, Japan may see many changes in their research activity..	Researchers in China have created embryos containing both human and monkey cells. The controversial project was conducted in China, rather than in the US where the project leader is based, "to avoid legal issues," according to the newspaper, and ultimately aims to grow viable organs for transplantation into humans.
Current Legislative Framework	Enacted law permits research on discarded embryos from in vitro fertilization procedures. However, it prohibits the creation of human embryos for research.	Permits the destruction of embryos for human embryonic stem cells harvests but only if the research: 1. Increases knowledge about the development of embryos, 2. Increases knowledge about serious disease, or 3. Enables any such knowledge to be applied in developing treatments for serious disease.	Both Italy and Germany have strict laws prohibiting the creation of chimeras via introducing animal cells to a human embryo or fusing human and animal embryos.	Permits researchers to produce and use human-animal chimeric embryos for basic research and disease modeling and for an alternative for organ transplantation in the future.	New measures outline requirements for such studies, including obtaining patients' informed consent and using clinical-grade stem cells that have been approved by an independent body. They say that stem-cell clinical studies can be carried out only at authorized hospitals, and they forbid the hospitals from charging recipients or advertising.

Embryo Research Generally

	USA	Canada	United Kingdom	EU (Italy, Germany)	Japan	China
Current Framework	Enacted law limited to federal funding conditions, e.g., **Prohibits** research in which embryo is created, destroyed, discarded, or subjected to risk or injury death above certain limit. **Permits** HHS-funded research on hESC from discarded embryos from *in vitro* fertilization procedures under certain conditions. *NIH Agency Policy:* **Prohibits** hESC from being introduced into non-human primate (NHP) blastocysts.	**Permits** research on discarded embryos from *in vitro* fertilization procedures. However, it prohibits the creation of human embryos for research.	**Permits** the destruction of embryos for human embryonic stem cells research but only if the research: 1. Increases knowledge about the development of embryos, 2. Increases knowledge about serious disease, or 3. Enables any such knowledge to be applied in developing treatments for serious disease. **Permits** production of hESC lines from surplus IVF embryos. **Permits** cloning of embryos to produce stem-cell lines for therapeutic purposes.	Germany: **Prohibits** surrendering, acquiring or using a human embryo from *in vitro* fertilization procedures or before embyro is implanted in the uterus, for a non-preservation purpose. However, Germany permits import of hESCs lines produced from surplus embryos from IVF before January 1, 2002. Italy: **Permits** clinical and experimental research on human embryos for diagnostic and therapeutic purposes to protect health and development of the embryo, if no available alternative methodologies exist.	**Permits** researchers to produce and use HACEs for basic research and disease modeling and for an alternative for organ transplantation in the future. Research limited to development, growth and implantation of embryos, that pertain to improvement of preservation techniques for Human Fertilized Embryos (“HFEs”), and contributions to improvement of assisted reproductive technology. Research HFEs shall not be transplanted into a human or animal uterus.	**Permits** research with specific requirements for such studies, including obtaining patients’ informed consent and using clinical-grade stem cells that have been approved by an independent body. Stem-cell clinical studies can be carried out only at authorized hospitals, and they forbid the hospitals from charging recipients or advertising.

Landscape: Broad Summary

- Most countries permit some embryo research, including hESCs.
- Most require consent from donors for research use and derivation of lines.
  - Many favor use of embryos from discarded IVF rather than *de novo* creation.
- Many set limits on source, use and outcomes (more, below).

Embryo Research and Chimeras

	USA	Canada	United Kingdom	EU (Italy, Germany)	Japan	China
Current Framework	*NIH Agency Policy:* **prohibits** hESC from being introduced into non-human primate (NHP) blastocysts. *NAS/NRC/IOM*: Independent review before hPSC introduced into NHPs or embryonic or perinateal animals with potential to develop into adult chimeras. (Congressional bills occasionally raise limits, including **prohibition** on chimeras with neural tissue primarily human, but none passed.)	**Prohibits** the creation of chimeras, which are defined as (human) embryos into which cells from other animals or humans have been introduced. Canada does **not prohibit** the creation of chimeric embryos by introducing **human cells to animal embryos**. • Main agencies responsible for funding scientific research in Canada expressly **prohibit** the creation of either form of chimeric embryo.	Enacted law **prohibits** placing a 'human admixed embryo' in an animal to develop. • The **Academy of Medical Sciences** recommends additional review for some categories of chimera research by an expert body (including research on brain function, behavior, or physical appearance) while rejecting some categories of research outright (including creation of human–nonhuman primate chimeras with 'human-like' brain function or breeding animals with human-derived germ cells).	Germany: **Prohibits** the creation of chimeras via introducing animal cells to a human embryo or fusing human and animal embryos. • The **German Ethics Council** recommends prohibiting additional kinds of chimera research (including the creation of chimeras capable of forming human gametes) and placing additional restrictions on the creation of human-animal brain chimeras, particularly involving nonhuman primates. Italy: Bans research on human embryos, including the use of embryos for deriving ES cell lines. The creation of human embryos for research purposes is also prohibited, however the use of imported hES cell lines is allowed.	**Permits** researchers to produce and use human-animal chimeric embryos for basic research and disease modeling and for an alternative for organ transplantation in the future. • The **Japanese Expert Panel on Bioethics** recommends repealing these prohibitions and proscribing a narrower range of practices, such as the generation of human brains in human–nonhuman primate chimeras	New measures outline requirements for such studies, including obtaining patients' informed consent and using clinical-grade stem cells that have been approved by an independent body. They say that stem-cell clinical studies can be carried out only at authorized hospitals, and they forbid the hospitals from charging recipients or advertising.

Embryo Research and “14-day rule”

	USA	Canada	United Kingdom	EU (Italy, Germany)	Japan	China
Current Framework	***Unofficial Limit*** dating to 1979 HHS (then, HEW) report on IVF, generally accepted by private organizations and professional societies.	**Prohibits** maintaining an embryo outside the body of a female person after the fourteenth day of its development following fertilization or creation, excluding any time during which its development has been suspended.	Human Fertilisation and Embryology Act 2008 **prohibits** keeping a human admixed embryo for longer than 14 days or beyond the appearance of the primitive streak.	Germany: **Prohibits** causing a human embryo to develop extracorporeally for a purpose other than bringing about a pregnancy. Italy: Silent.	Japan specifically **prohibits** a “Human Fertilized Embryo,” (defined as an Embryo produced by fertilization between a human Sperm and a human Unfertilized Egg, including each Embryo which is produced successively by single or multiple splitting of such an Embryo and is not a Human Split Embryo) may be handled, but only during the period until the primitive streak starts to form. However, with regard to Human Fertilized Embryos in which the primitive streak does not start to form during the 14-day period from fertilization, these shall not be handled after the 14 days have elapsed.	*In vitro* culture period of embryos obtained from IVF, human somatic cell nuclear transfer, parthenogenesis or genetic modification techniques, are **prohibited** from exceeding 14 days starting from the day when fertilization or nuclear transfer is performed.

Use of Embryos for Research

Nation	Regulatory Impact	Relevant Language
Germany	Creation of embryos prohibited for research purposes.	"§ 1 Abusive use of reproductive techniques (1) Anyone who is punished with a prison sentence of up to three years or a fine 1. transfers a foreign unfertilized egg to a woman, **2. undertakes to artificially fertilize an egg cell for any purpose other than to bring about a pregnancy of the woman from whom the egg cell originates,** 3. undertakes to transfer more than three embryos to a woman in one cycle, 4. undertakes to fertilize more than three egg cells within one cycle by intratubar gamete transfer, 5. attempts to fertilize more eggs from a woman than can be transferred to her in one cycle, 6. removes an embryo from a woman before it is implanted in the uterus in order to transfer it to another woman or to use it for a purpose that does not serve its preservation, or 7. undertakes artificial insemination or transferring a human embryo to a woman who is willing to leave her child permanently after the birth to third parties (surrogate mother)."
Japan	Creation of embryos permitted	"For the time being, the research shall **be limited to that pertaining to development, growth and implantation of embryos,** that pertaining to improvement of preservation techniques for Human Fertilized Embryos, and other research that contributes to improvement of assisted reproductive technology."

Use of Embryos for Research

Nation	Regulatory Impact	Relevant Language
United Kingdom	Creation of embryos permitted.	"**Activities For Which Licenses May Be Granted**. A licence under this paragraph may authorise any of the following— **(a) bringing about the creation of embryos in vitro,** and (b) keeping or using embryos, for the purposes of a project of research specified in the licence."
Switzerland	Creation of embryos prohibited for research purposes.	Oviedo Convention has been ratified: "Art. 18: Research on embryos in vitro. 1. Where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo. 2. The creation of human embryos for research purposes is prohibited."

Importation or Exportation of Embryos for Research

Nation	Regulatory Impact	Relevant Language
China	Collaboration required for import or export	Article 7 of the Human Genetic Resource Regulations prohibits Foreign Entities from collecting or preserving Chinese human genetic resources; nor are they allowed to supply human genetic resources overseas (the 2019 Human Genetic Resource Regulations require a prior record filing with the MOST when exporting human genetic information out of China, and human genetic materials is subject to even stricter supervision). However, Foreign Entities are permitted to collaborate with Chinese research institutions, higher education institutions, medical institutions, and enterprises to utilize Chinese human genetic resources for scientific research, subject to complying with Chinese laws regulations and other provisions and obtaining prior approval from Ministry of Science and Technology.
Japan	Collaboration required for import or export.	A Research Institution **shall not transfer Human Fertilized Embryos used in research to other institutions**. However, in cases where research is conducted collaboratively at multiple Research Institutions, Human Fertilized Embryos used in research may be transferred, but only between these Research Institutions.

Importation or Exportation of Embryos for Research

Nation	Regulatory Impact	Relevant Language
Saudi Arabia	Import or export may be permitted.	Commercially available induced pluripotent stem cells can also be imported from scientifically recognized sources. It is prohibited to import the following stem cells: 1. Stem cells obtained from the insemination using a donor ovum and a donor sperm, performed to extract stem cells. 2. Stem cells obtained from deliberately aborted fetuses.
United Kingdom	Import or export may be permitted for therapeutic purposes only.	Authorizes any person to whom a license applies to **receive gametes, embryos or human admixed embryos from outside the United Kingdom or to send gametes, embryos or human admixed embryos outside the United Kingdom.** Purpose of importing the gametes or embryos concerned is to enable them to be used to provide treatment services, namely medical, surgical or obstetric services for the purpose of assisting a woman to carry a child or to be stored for such a purpose in the future.

Importation or Exportation of Embryos for Research

Nation	Regulatory Impact	Relevant Language
Ukraine	Import or export of human embryos prohibited.	Prohibition of human reproductive cloning Human reproductive cloning is banned in Ukraine. This Law does not apply to the cloning of other organisms."

Participant (Donor) Informed Consent

Nation	Regulatory Impact	Relevant Language
Canada	Specific research purposes must be discussed prior to obtaining consent.	“No person shall make use of an *in vitro* embryo **for any purpose** unless the donor has given written consent, in accordance with the regulations, to its use for that purpose.”
Japan	Specific research purposes must be discussed prior to obtaining consent	“Consent regarding the provision and handling of a Human Fertilized Embryo, which a Donor gives on the basis of his/her discretion after receiving adequate prior explanations from a researcher, etc. with regard to the research and after **understanding the significance, objectives and method of the research, the expected results and the disadvantages**.”
Switzerland	Specific research purposes must be discussed prior to obtaining consent.	"...surplus embryo may only be **used for the derivation of embryonic stem cells** if written consent has been freely given by the couple concerned. Before such consent is given, the couple must be provided with adequate information, verbally and in writing, in a comprehensible form, concerning the use of the embryo."

Participant (Donor) Informed Consent

Nation	Regulatory Impact	Relevant Language
United Kingdom	Specific research purposes must be discussed prior to obtaining consent.	"A consent to the use of any embryo must specify one or more of the following purposes— (a) use in providing treatment services to the person giving consent, or that person and another specified person together, (b) use in providing treatment services to persons not including the person giving consent, (ba) use for the purpose of training persons in embryo biopsy, embryo storage or other embryological techniques, or (c) use for the purposes of any project of research, and may specify conditions subject to which the embryo may be so used. …A consent to the use of any human admixed embryo **must specify use for the purposes of any project of research and may specify conditions subject to which the human admixed embryo may be so used**. …A consent to the use of a person's human cells to bring about the creation *in vitro* of an embryo or **human admixed embryo** is to be taken unless otherwise stated to include consent to the use of the cells after the person's death."
Ukraine	Prior Informed Consent required.	"...with clinical justification and with the consent of the patient."

Permitted Period for Use of Research Embryos

Nation	Regulatory Impact	Relevant Language
Switzerland	Up to 7 days.	"…using a surplus embryo for any purpose other than the derivation of embryonic stem cells, or importing or exporting such an embryo, or deriving stem cells from a surplus embryo after the seventh day of its development, or placing in a woman a surplus embryo used for stem cell derivation (Art. 3 para. 2)."
Japan	Time restriction only placed on embryos that are produced by fertilization between a human sperm and a human unfertilized egg.	"A Human Fertilized Embryo may be handled, but only during the period until the primitive streak starts to form. However, with regard to Human Fertilized Embryos in which the primitive streak does not start to form during the 14-day period from fertilization, these shall not be handled after the 14 days have elapsed. In cases where a Human Fertilized Embryo is stored frozen, this period of frozen storage shall not be included in the period of handling."

Permitted Period for Use of Research

Nation	Regulatory Impact	Relevant Language
United Kingdom	The lesser of 14 days or appearance of the primitive streak.	"(3) A licence cannot authorise— (a) keeping or using an embryo after the appearance of the primitive streak, (b) placing an embryo in any animal, or (c) keeping or using an embryo in any circumstances in which regulations prohibit its keeping or use, F4... (4) For the purposes of subsection (3)(a) above, the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with [F5the day on which the process of creating the embryo began], not counting any time during which the embryo is stored."
Sweden	Up to 14 days.	"Experiments for the purpose of research or treatment on fertilised eggs and eggs used for somatic cell nuclear transfer may be carried out no longer than up to and including the fourteenth day after fertilisation or cell nuclear transfer respectively."

Reproductive and Therapeutic Cloning

Nation	Regulatory Impact	Relevant Language
Canada	Prohibits reproductive cloning only.	No person shall knowingly create a human clone by using any technique, or **transplant a human clone into a human being or into any non-human life form or artificial device.**
China	Prohibits reproductive cloning only.	All research activities related to human embryonic stem cells shall comply with the following norms: (1) Embryos obtained from IVF, human somatic cell nuclear transfer, parthenogenesis or genetic modification techniques, its in vitro culture period shall not exceed 14 days starting from the day when fertilization or nuclear transfer is performed. (2) It **shall be prohibited to implant embryos created by means described above into the genital organ of human beings or any other species**.
Germany	Prohibits all forms of cloning (reproductive and therapeutic).	Anyone who (1) **artificially causes** a human sperm cell to invade a human egg cell, or (2) **artificially transfers** a human sperm cell to a human egg cell, without wanting to bring about a pregnancy of the woman from whom the egg cell originated.

Reproductive and Therapeutic Cloning

Nation	Regulatory Impact	Relevant Language
Japan	Prohibits reproductive cloning only.	Prohibition of Transplantation into Uteri (1) Human Fertilized Embryos used in research **shall not be transplanted into a human or animal uterus.** (2) Research shall not be conducted in a room that is equipped with facilities allowing Human Fertilized Embryos to be transplanted into a human or animal uterus.
Sweden	Prohibits reproductive cloning only.	Gene therapy. Section 3. Experiments for the purposes of research or treatment **that entail genetic changes that can be inherited in humans may not be carried out**. Section 4.Treatment methods that are intended to bring about genetic changes that can be inherited in humans may not be used.

Reproductive and Therapeutic Cloning

Nation	Regulatory Impact	Relevant Language
Switzerland	Prohibits all forms of cloning (reproductive and therapeutic).	Art. 119 Reproductive medicine and gene technology involving human beings (1) Human beings shall be protected against the misuse of reproductive medicine and gene technology. (2) The Confederation shall legislate on the use of human reproductive and genetic material. In doing so, it shall ensure the protection of human dignity, privacy and the family and shall adhere in particular to the following principles: **a. All forms of cloning and interference with the genetic material of human reproductive cells and embryos are unlawful.** b. Non-human reproductive and genetic material may neither be introduced into nor combined with human reproductive material. c. (1) The procedures for medically-assisted reproduction may be used only if infertility or the risk of transmitting a serious illness cannot otherwise be overcome, but not in order to conceive a child with specific characteristics or to further research; the fertilisation of human egg cells outside a woman's body is permitted only under the conditions laid down by the law; (2) no more human egg cells may be developed into embryos outside a woman's body than are required for medically-assisted reproduction. d. The donation of embryos and all forms of surrogate motherhood are unlawful.

Reproductive and Therapeutic Cloning

Nation	Regulatory Impact	Relevant Language
Ukraine	Prohibits reproductive cloning only.	Conservation of the gene pool of the people of Ukraine: In the interests of preserving the gene pool of the people of Ukraine, preventing the demographic crisis, ensuring the health of future generations and preventing hereditary diseases, the state implements a set of measures aimed at **eliminating factors that adversely affect the human genetic apparatus, as well as creates a system of state genetic monitoring,** organizes medical and genetic care, promotes the enrichment and dissemination of scientific knowledge in the field of genetics and demography. Medical intervention, which can cause a disorder of the human genetic apparatus, is prohibited. Indeterminate
United Kingdom	Prohibits reproductive cloning only.	Prohibitions in connection with embryos (2) **No person shall place in a woman—** **(a) an embryo other than a permitted embryo (as defined by section 3ZA).** An embryo is a permitted embryo if— (a) it has been created by the fertilisation of a permitted egg by permitted sperm, (b) no nuclear or mitochondrial DNA of any cell of the embryo has been altered, and (c) no cell has been added to it other than by division of the embryo's own cells.

Current Regulatory Framework: Animals for Research

	Canada	United Kingdom	EU (Italy, Germany)	Japan	China
Current Legislative Framework	Enacted federal law includes suffering as a separate concept from pain and injury, which applies to all animals and birds. Canadian provinces and territories have their own laws to protect animals from cruelty. • Civil Code of Quebec explicitly states that animals are sentient. No specific regulations at federal level regarding this use of animals. In guidelines and policies, the Canadian Council on Animal Care only acknowledges the importance of the Three Rs principles in research – Replacement, Reduction, Refinement.	Enacted law recognizes that animals can suffer, but no explicit reference to animal sentience. Scotland established first independent Animal Welfare Commission in the UK, to consider scientific and ethical evidence regarding welfare needs of sentient animals and what improvements can be made. Animals (Scientific Procedures) Act 1986 regulates procedures carried out on protected animals for scientific or educational purposes which have the potential to cause pain, suffering, distress or lasting harm. Article 4 enshrines the Three Rs principles in legislation – Replacement, Reduction, Refinement.	European Union (EU) treaty explicitly recognizes animal sentience and requires that Member States 'pay full regard to the welfare requirements of animals' in formulating and implementing European Union policies on agriculture, fisheries, transport, research and technological development. Germany: Animal Protection Act recognizes animal welfare and the suffering of animals and incorporates the requirements of EU legislation. Animal sentience is not specifically referred to in the Act. It also details minimum standards for the welfare of animals used in scientific research. Italy: Legislative Decree No. 189/2004 implicitly recognizes that animals can suffer physically and mentally, however, it does not formally recognize animal sentience. Regarding animals used in scientific research, it explicitly aims to avoid and reduce the number of animals used in experimentation.	Act on Welfare and Management of Animals, most recently amended in 2014, states in the fundamental principle of the Act that 'no person shall destroy, injure or inflict cruelty on animals' as they are living beings. Enforcement mechanisms only apply to a list of specified species of animals, all of which are domestic animals (companion and farm animals). The Act does specifically address welfare issues associated with the use of animals in research and incorporate some of the principles of the Three Rs principles. However, there does not appear to be any system of inspection for laboratories or any formal mechanism to achieve compliance with the relevant legislation and guidance.	There is no single law addressing animal protection, animal welfare issues are addressed in several places in lower level legislation. Current animal protection laws demonstrate first steps towards legal protection of animal sentience. Guidance on Kind Treatment of Laboratory Animals (2006) refers to elements of animal sentience for animals used in experiments. The Guidance only applies to animals used in research, however it demonstrates a movement away from a system which takes human rights as the basis for protection of animals.

Safety, Efficacy, Quality Control

- The European Medicines Agency and the Food and Drug Administration have set Good Manufacturing Practice (GMP) guidelines for safe and appropriate stem cell transplantation.
- Marketing Approval processes and procedures *should* address these concerns.

US Law – Future Questions

Current law (codified at 42 USC 289 g-2(c)): Prohibits, through fines and imprisonment, research activities with certain tissues, which, though not yet interpreted may be a concern at some future time.

"Solicitation or acceptance of tissue from fetuses gestated for research purposes

It shall be unlawful for any person or entity involved or engaged in interstate commerce to—

(1) solicit or knowingly acquire, receive, or accept a donation of human fetal tissue knowing that a human pregnancy was deliberately initiated to provide such tissue; or

(2) knowingly acquire, receive, or accept tissue or cells obtained from a human embryo or fetus that was gestated in the uterus of a nonhuman animal." (emphasis added)

Key Issues

- Participant Consent from Tissue Donors
- Source of material, *e.g.,* stem cells, embryos
  - Limits on sources
  - Limits on use
  - Limits on scope of research
- Independent Review of Experiments
- Protections for Animals
- Safety and Efficacy, Pre-market Approval, Quality Control
- Enforcement Consistency – *are laws enforced consistently or randomly*?

Regulatory Gaps and Opportunities

- Reach of Federal Law; Diversity of State Law
- Limits:
  - Risk that neural organoid presents evidence of brain activity, develops some form of sentience;
    - Basic neurological functions, cognitive functions, active pain pathways, self-awareness or consciousness (minute though it may be at present);
    - Where draw line?
      - When there is no reason to think the organoid will have consciousness at all, should there be any limit?
      - Interests of resulting organoid or chimera
- Communication of potential and results, public engagement
  - “Democratic Deliberation”

Thank You

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