

SINGAPORE



LEGAL AND REGULATORY FRAMEWORKS AND THEIR IMPLICATIONS FOR HUMAN GENE EDITING IN CLINICAL AND RESEARCH APPLICATION

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QUESTIONS FOR PRESENTERS

- Please describe any existing or proposed regulations in your country that would regulate gene editing? – **Slide 8**
- Does your country's regulations distinguish between somatic and germline applications? Between therapeutic and enhancement applications? – **Slide 12**
- Does your country's regulatory framework for assisted reproductive technologies apply to or have implications for gene therapy in general, CRISPR in particular? – **Slides 8, 10-19**
- Does your country's regulatory system incorporate, expressly or implicitly, risk management principles such as the precautionary principle, prevention, cost-benefit analysis, de minimis risk, or others? – **Slide 8 (implicitly)**
- How important is international coordination in influencing your country's policies on gene editing? What organizations or institutions would be influential to your country for encouraging international coordination – **Slides 4-6**

STATUTORY LAWS AND REGULATIONS

- [Singapore Statutes Online](#)
 - See the Human Biomedical Research Act (2015)
 - Human Cloning and Other Prohibited Practices Act (2004, Rev 2005)

BAC SINGAPORE (FROM THE BAC WEBSITE)



The **terms of reference** of the Bioethics Advisory Committee are:

1. To examine **ethical, legal and social issues arising from research on human biology and behaviour and its applications**; and
2. To **develop and recommend policies to the Singapore Government**, on legal, ethical and social issues, with the aim of protecting the rights and welfare of individuals, while allowing the biomedical sciences to develop and realise their full potential for the benefit of humankind.

The BAC is a policy advisory body, not an executive body. It has no supervisory or regulatory power. It:

- a) Considers and recommends policy in biomedical research ethics, **taking into account international best practice** and locally relevant concerns or issues;
- b) Supports and implements public education initiatives in bioethics, alone or in collaboration with other agencies;
- c) Liaises with other similar bodies elsewhere and engages in bioethics issues internationally** through such activities as conference participation, BAC visits to overseas centres, and the organising of events relevant to advancing bioethics; and
- d) Publishes reports, consultation papers, or other documents reflecting its activities.

It does not make any recommendation in respect of clinical medical ethics

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(FROM THE BAC WEBSITE)

The principles expressed in these documents are generally endorsed by the BAC, and have been used to derive [BAC's own set of principles](#).

- [The Nuremberg Code](#) (1949)
- [The Declaration of Helsinki: Ethical Principles for Research Involving Human Subjects](#) (1964, Revised 2008)
- [The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research](#) (1979)
- [The International Ethical Guidelines for Biomedical Research Involving Human Subjects](#) (2002)
- [The UNESCO Universal Declaration on Bioethics and Human Rights](#) (2005) (Note: Singapore is a member of IGBC UNESCO and the BAC Chair is a Vice Chair of IBC UNESCO)

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

NMEC SINGAPORE



- The National Medical Ethics Committee (NMEC) was set up in January 1994 by the Ministry of Health. It **aims to identify and study ethical issues relating to medical practice and research in Singapore and provide an ethical framework for medical practitioners.**
- The NMEC has **no statutory powers. Nevertheless, it serves as the national authority which provides advice to the Ministry of Health and other agencies on prevailing ethical issues.** The ethical guidelines which have been drawn up for various clinical situations are intended to facilitate medical professionals in the process of making sound ethical decisions in clinical practice and medical research.

REGULATORY STATUS OF BAC AND NMEC



- BAC's and NMEC's Guidelines are not hard-coded laws, but are used by ethics committees and healthcare and research institutions, and regularly reviewed and updated in light of current developments.

REGULATION OF GENE EDITING

- No regulations exist for gene editing and CRISPR technology at this time.
- However, note: **NMEC: Ethical Guidelines for Gene Technology (2001)**

- **Prohibit** germline modification or inheritable genetic modification; and
- **Allow** somatic gene therapy to be carried out **under stipulated conditions.**

- **See:**

8. Categories of gene therapy

–8.1 A major distinction must first be made between somatic and germ-line gene therapy. **Somatic gene therapy** is the correction of genetic defects in postnatal somatic cells in the body. This approach is fundamentally not different from any form of organ transplantation or even blood cells transfusion. Genetic changes thus introduced are confined to the subject whose cells are modified.

- ❑ Singapore National Medical Ethics Committee: *Ethical Guidelines for Gene Technology (2001)*
- ❑ Singapore Bioethics Advisory Committee: *Genetic Testing and Genetic Research (2005)*

MORATORIUM ON CLINICAL APPLICATION OF GERMLINE MODIFICATION

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

MORATORIUM ON CLINICAL APPLICATION OF GERMLINE MODIFICATION

National Medical Ethics Committee: *Ethical Guidelines for Gene Technology* (2001)

https://www.moh.gov.sg/content/dam/moh_web/Publications/Guidelines/National%20Medical%20Ethics%20Committee%20Guidelines/2001/GeneGuidelines.pdf

- 8.2.2. We strongly advocate that germ-line gene therapy with the result of passing on the genetic changes to the offspring should not be contemplated presently for the following reasons:
 - (a) The ethical issue of whether and when a foetus becomes a patient remains highly controversial. Does the pre-viable foetus have as much an independent right as a patient (subject) as a viable foetus?
 - (b) The potential risks to the mother during *in-utero* gene transfer have not been hitherto studied.

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

NATIONAL MEDICAL ETHICS COMMITTEE: *ETHICAL GUIDELINES FOR GENE TECHNOLOGY* (2001)



- 8.2.2 continued
- (c) Given our limited knowledge on the long-term safety and risks of gene therapy, germ-line gene therapy is fraught with the risk of unanticipated, deleterious alterations in the genetic code that may be passed on from generation to generation.
- (d) As we are unaware of all the activities of a particular gene, one may select against and gradually eliminate alleles from the human gene pool that benefit humans in potentially unknown ways when they appear in the heterozygous state.
- (e) The line between germ-line gene therapy and eugenics is a tenuous one.

SOMATIC V. GERMLINE APPLICATIONS



NATIONAL MEDICAL ETHICS COMMITTEE: *ETHICAL GUIDELINES FOR GENE TECHNOLOGY* (2001)

https://www.moh.gov.sg/content/dam/moh_web/publications/guidelines/national%20medical%20ethics%20committee%20guidelines/2001/geneguidelines.pdf

8. Categories of gene therapy

•8.1 A major distinction must first be made between somatic and germ-line gene therapy. *Somatic gene therapy* is the correction of genetic defects in postnatal somatic cells in the body. This approach is fundamentally not different from any form of organ transplantation or even blood cells transfusion. Genetic changes thus introduced are confined to the subject whose cells are modified.

•8.2.1. In contrast, *germ-line gene therapy*, which involves the insertion of foreign genes into fertilised eggs or very early embryos, can result in the transmission of the genetic changes to the offspring in the subsequent generations.

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Passing reference:



THERAPEUTIC V. ENHANCEMENT APPLICATIONS

“8.2.2 (e) The line between germ-line gene therapy and eugenics is a tenuous one.”

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

MORATORIUM ON CLINICAL APPLICATION OF GERMLINE MODIFICATION

- Bioethics Advisory Committee: *Genetic Testing and Genetic Research* (2005)

<http://www.bioethics-singapore.org/index/publications/reports/171-genetic-testing-and-genetic-research.html>

Germline Genetic Modification

- Germline genetic modification is a type of gene technology that involves the alteration of a person's genetic makeup in a manner that is permanent and can be transmitted to his or her offspring. It is one of the rising gene technologies applicable at the preimplantation stage of an embryo. We note that germline genetic modification may also be brought about inadvertently in gene therapy or through other experimental techniques.
- **We are of the view that the clinical practice of germline genetic modification should not be allowed at this time.** Germline genetic modification is at present still experimental and will require substantial research to establish its feasibility and safety in clinical application. In addition, the potentially great impact on future generations presents serious ethical concerns. **We will monitor progress in germline genetic modification and reassess its clinical applicability at an appropriate time in the future.**

□ Bioethics Advisory Committee: *Ethics Guidelines for Human Biomedical Research (2015)*

[N.B: published before passage of Human Biomedical Research Act]

□ Human Biomedical Research Act (2015)

RESEARCH INVOLVING GERMLINE MODIFICATION IN HUMAN EMBRYOS

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

RESTRICTIONS ON RESEARCH INVOLVING HUMAN GAMETES AND EMBRYOS

Bioethics Advisory Committee: Ethics Guidelines for Human Biomedical Research (2015)

[N.B: published before passage of Human Biomedical Research Act]

<http://www.bioethics-singapore.org/index/publications/reports/86-reports/ethics-guidelines-for-human-biomedical-research.html>

- 5.23 The creation of human embryos specifically for research can only be justified when there is strong scientific merit in and potential medical benefit from such research. **The Human Cloning and Other Prohibited Practices Act prohibits the development of a human embryo created other than by fertilisation of human egg by human sperm, for a period of more than 14 days, excluding any period when the development of the embryo is suspended.** Commercial trading in human eggs, human sperm and human embryos is also prohibited.
- 5.24 The supply and use of human gametes and embryos is governed by the Human Cloning and Other Prohibited Practices Act (Cap. 131B). Researchers should also comply with the requirements stipulated in MOH's 2011 Licensing Terms and Conditions (LTC) on Assisted Reproduction (AR) Services imposed under Section 6(5) of the Private Hospitals and Medical Clinics Act.

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

Bioethics Advisory Committee: Ethics Guidelines For Human Biomedical Research (2015) continued



- 5.25 **Under the LTC, written approval from the Director of Medical Services must be obtained for all research involving human embryos and human oocytes** (including those obtained from excised ovarian tissue). This requirement extends to human-animal combination gametes or embryos, which are those containing both human and animal genetic or non-genetic material and includes an embryo created by the fertilisation of human and animal gametes.
- 5.32 **Human embryos created for research through in vitro fertilisation of human eggs by human sperm, or created through any form of cloning technology, should not be allowed to develop beyond 14 days in vitro.**
- 5.33 Human embryos created for research through in vitro fertilisation of human eggs by human sperm, or created through any form of cloning technology, should not be implanted into the body of any human or animal.
- 5.35 No one should be under a duty to participate in any manner of research involving human gametes or embryos, including human-animal combination embryos, to which he or she has a conscientious objection.

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

Human Biomedical Research Act (2015)

<http://statutes.agc.gov.sg/aol/search/display/view.w3p;ident=f5e3b0d8-e3e5-496b-b1e3-1cd8d83049eb;page=0;query=compid%3af5e3b0d8-e3e5-496b-b1e3-1cd8d83049eb;rec=0;resurl=http%3a%2f%2fstatutes.agc.gov.sg%2faol%2fbrowse%2ftitlresults.w3p%3bletter%3dh%3btype%3dacts%3bpub%3blegis>



The Fourth Schedule of the HBRA (2015) restricts human biomedical research involving human eggs or human embryos. In addition,

• *Restricted human biomedical research*

• **31. —(1) No research institution or person can conduct, supervise or control any restricted human biomedical research specified in the Fourth Schedule except in accordance with such requirements as the Minister may prescribe** and such prescribed requirements are in addition to and not in lieu of the requirements in this Act.

(2) Without prejudice to the generality of subsection (1), the additional requirements which may be prescribed for the purposes of subsection (1) may include the following:

- (a) that the Director should be notified of the conduct of such restricted human biomedical research;
- (b) that the restricted human biomedical research should be carried out only under, and in accordance with the conditions of approval obtained from the Director or a public officer authorised by the Minister

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

Human Biomedical Research Act (2015) continued



- (c) that the restricted human biomedical research should be reviewed by an institutional review board, or such other committee as may be prescribed, comprising members with certain specified qualifications;
- (d) that the restricted human biomedical research should be conducted only by certain specified persons;
- (e) that the appropriate consent in a restricted human biomedical research be obtained from the research subject who has capacity to give consent in person and not from a person authorised under Part 3 to give consent on the subject's behalf;
- (f) that the restricted human biomedical research should be carried out only at certain specified premises;
- (g) that the restricted human biomedical research should or should not be conducted in any specified manner.
- (4) Any person who contravenes subsection (1) or (3) shall be guilty of an offence and shall be liable on conviction to a fine not exceeding \$100,000 or to imprisonment for a term not exceeding 10 years or to both.

BAC Workgroup

MITOCHONDRIAL REPLACEMENT TECHNOLOGIES

HUMAN GENE EDITING, PARIS MEETING 29-APRIL-2016

BAC's Current Project: Mitochondrial Replacement Technology



- Following regulatory changes in the UK legislating the clinical application of mitochondrial replacement techniques, BAC has formed a Germline Modification Working Group (WG)
- A public consultation paper is being drafted by the WG
- Some issues that WG may wish to explore include:
 - The difference between (modifying) nuclear vs mitochondrial DNA
 - The welfare of the future child and later generations
 - Issues of reproductive autonomy
 - Potential risks and expected benefits of mitochondrial replacement, and determination of the risk-benefit threshold for first-in-human trials
 - Issues of distributive justice

THANK YOU

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