MINISTRY OF HEALTH
SINGAPORE

Human Biomedical Research Act

Regulatory Framework : Scope & Highlights

9 Dec 2016

HUMAN BIOMEDICAL RESEARCH ACT

- Passed by Parliament in August 2015

  …but has not been brought into operation yet…

- Gives legal effect to two separate, but related, regulatory frameworks

(A) Human Biomedical Research (HBR) Framework

– regulates conduct of "human biomedical research"

(B) Human Tissue Framework

– regulates dealings in "human tissue"

– prohibits commercial trading in "human tissue"

SCOPE OF REGULATED RESEARCH

- "Human biomedical research" covers 2 broad areas :

1. Human subject research that have certain intended purposes and involve certain methodologies, per section 3(2)

"Any research that is intended to study –

(a) the prevention, prognostication, diagnosis or alleviation of any disease, disorder or injury affecting the human body; **or**

(b) the restoration, maintenance or promotion of the aesthetic appearance of human individuals through clinical procedures or techniques; **or**

(c) the performance or endurance of human individuals,

where the research involves –

(i) subjecting an individual to any intervention (including any wilful act or omission) that has a physical, mental or physiological effect (whether temporary or permanent) on the body of the individual; **or**

(ii) the use of any individually-identifiable biological material obtained from the human body; **or**

(iii) the use of any individually-identifiable health information."

SCOPE OF REGULATED RESEARCH

- "Human biomedical research" covers 2 broad areas :

2. Certain types of 'sensitive' embryological and stem cell research, as per section 3(3)

"Any research that involves –

(a) human embryos or human gametes;

(b) cytoplasmic hybrid embryos;

(c) the introduction of any human-animal combination embryo into an animal or a human;

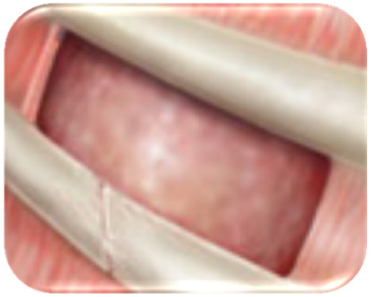
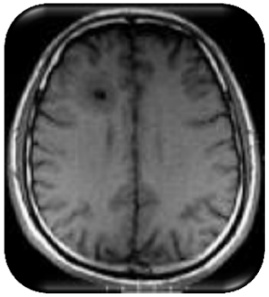
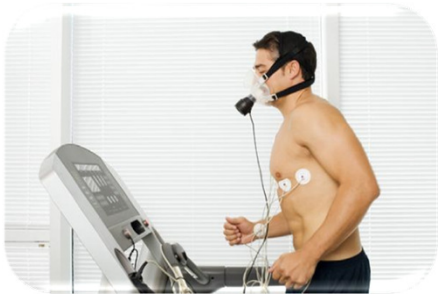
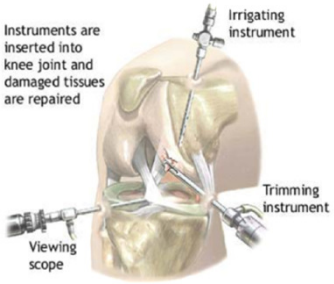
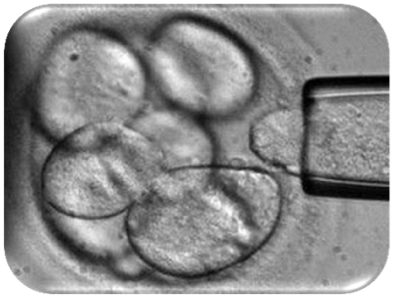
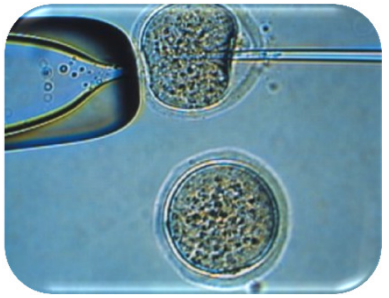
(d) the introduction of human stem cells or human neural cells into an animal at any stage of development; or

(e) any entity created as a result of any process referred to in paragraph (c) or (d)."

Note that even if such tissues are non individually-identifiable, the research still falls within the scope of HBR Act.

SCOPE OF REGULATED RESEARCH

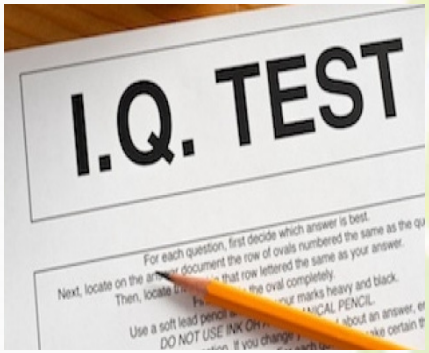
- Examples of "human biomedical research"

Bio-engineered tissue grafts 	**Diagnostic imaging** 	**Endurance testing** 
Surgical techniques 	**I-ID human cells/tissues** 	**I-ID health information** 
Human eggs 	**Human embryos** 	**Cytoplasmic hybrid embryos** 

SCOPE OF REGULATED RESEARCH

- Some types of research or studies are excluded from scope of "human biomedical research" – specified in the Second Schedule

Normal psychological responses and behaviours



Measurement of human intelligence

"Clinical trials" regulated under Medicines Act or Health Products Act

Public health research permitted and/or required under other laws

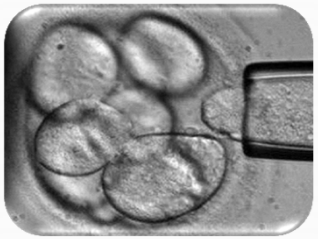
SCOPE OF REGULATED RESEARCH

- In general, all "human biomedical research" will be subject to the general controls on HBR
- Additionally –
  - some HBR classified as "restricted human biomedical research"
    - specified in the Fourth Schedule
    - subject to additional controls (e.g. requires specific approval from MOH), per section 31
  - some HBR classified as "prohibited human biomedical research"
    - specified in the Third Schedule
    - not allowed to be conducted at all, per section 30

SCOPE OF REGULATED RESEARCH

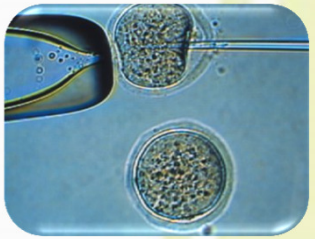
- Various types of "restricted" HBR specified in the Fourth Schedule

Human Embryo



Human Egg

Cytoplasmic Hybrid



PROHIBITED

Development beyond 14 days

Animal Chimeras

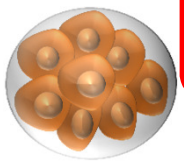
Human Stem Cells

Lineage Specific Stem Cell

Multipotent Stem Cell

Pluripotent Stem Cell

All types of human stem cells

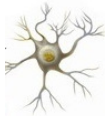


Implantation into uterus of animal or human

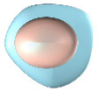
PROHIBITED

Animal embryo

Animal foetus



Human Neurons



Pluripotent Stem Cell

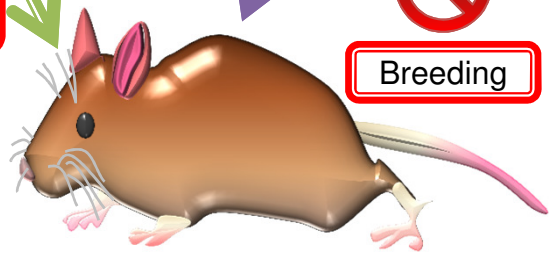
Brain

Into brain of great apes

PROHIBITED

PROHIBITED

Breeding



Adult animal

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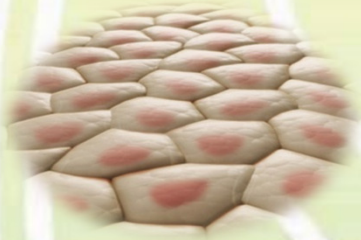
SCOPE OF TISSUE REGULATION

Regulated Tissue

- "Human biological material" and "human tissue" defined in section 2

- "Human biological material"

  "…means any biological material obtained from the human body that consists of, or includes, **human cells**"



- "Human tissue"

  "…means any human biological material…

  …**excludes** [those] material specified in the First Schedule"

  1. Hair shaft, cut without dermal hair root or follicle.
  2. Nail plate, cut without underlying dermal tissue.
  3. Naturally-excreted bodily fluids and waste products e.g. saliva, sweat, urine, faeces.
  4. Human biological material that is not individually-identifiable, and has been processed in such a manner that its functional, structural and biological characteristics are substantially manipulated…

SCOPE OF TISSUE REGULATION

Regulated Tissue

- "Substantially manipulated" human biological material (HBM)
  - undergone more than just minimal manipulation
- HBM is **not** deemed to be substantially manipulated merely because it has been processed by any (combination) of the following methods:
  - cutting, grinding, shaping
  - centrifugation
  - soaking in antibiotic or antimicrobial solutions
  - sterilization, low-level irradiation
  - cell separation, concentration or purification
  - filtering
  - lyophilisation
  - freezing, cryopreservation, vitrification

List adapted from EU Directive Regulation (EC) No. 1394/2007 – Annex I

- HBM that has been substantially manipulated (e.g. culture expanded, immortalized cell lines, transfected cells/tissues) and is no longer individually-identifiable, is not considered to be "human tissue" under the Act.

SCOPE OF TISSUE REGULATION

Regulated Activities

- The regulatory requirements of the tissue framework will apply generally to the following activities relating to "human tissue"
  - removing human tissue from donor's body for use in research
  - storing human tissue for subsequent use in research
  - supplying human tissue (including supplying to recipient outside Singapore) for use in research
  - using human tissue in research
  - using human tissue that had been removed, stored or supplied for use in research, for any purpose other than research
- More broadly, the tissue framework generally prohibits commercial trading of human tissue regardless of purpose – ref. sections 32 & 33
  - corresponds to existing prohibition against commercial trading of:
    - human organs and blood – in Human Organ Transplant Act
    - human eggs, sperm and embryos – in Human Cloning and Other Prohibited Practices Act

HBR FRAMEWORK

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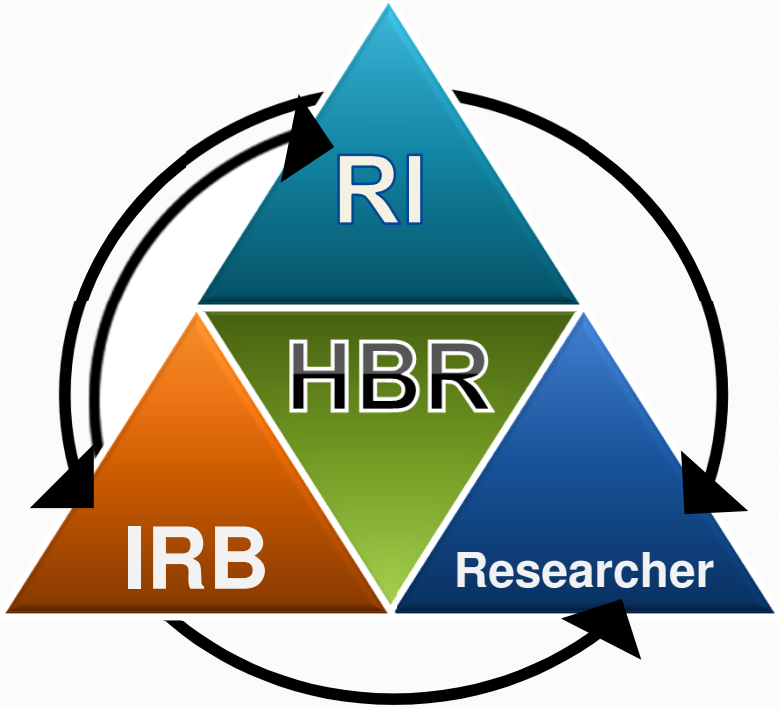
Section 22

KEY ENTITIES OF FRAMEWORK



Research Institution (RI)

..a body of persons, whether corporate or unincorporate or other organisation, or ministry or department of the Government, who or which –

(a) engages (through contractual or other arrangements) one or more researchers to conduct human biomedical research; and

(b) exercises supervision and control over human biomedical research conducted by the researchers he or it has engaged

***RI may not be the research site.**

Researcher

A natural person who conducts HBR under the supervision and control of a "RI"

Institutional Review Board (IRB)

A board appointed by RI to perform ethics review of HBR & other review functions.

Self-Accountability Framework

Sections 23, 24

FUNCTIONS & DUTIES OF RI

Must be in **Singapore** & have **at least 2 individuals** ordinarily resident in Singapore

1. ✓ Supervise, review & proactively monitor the safe and ethical conduct of the research

2.
- ✓ Notify MOH before the commencement of any HBR
- ✓ Annual declaration of compliance
- ✓ Report **Serious Adverse Events**

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3. **IRB**

✓Appoint **at least one IRB** to review the HBR under its supervision & be responsible for its proper functioning & decision making

4.

✓ Establish a data and safety monitoring board if the IRB considers that it is necessary

5.

✓ Appoint **Person-In-Charge,** develop internal policies, standards and systems for the proper conduct of any HBR

Section 22

DUTIES OF RESEARCHERS

RI

1.

2. Protocol approved

IRB

Must come under the supervision of an RI

3. *Appropriate Consent obtained

Restricted Research Schedule IV

MINISTRY OF HEALTH SINGAPORE

4. Approved by MOH Advisory Committee

- **Amendment must be re-approved**
- **Must not deviate from the research that had been approved**
- **Must protect subject or donor confidentiality** Section 27

RESEARCH STARTS

HUMAN TISSUE FRAMEWORK

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Section 37

CONSENT – THE KEY REQUIREMENT

General Rules : ***-For removal, storage, supplying and use of tissues-***

1. There must be appropriate consent.
2. The activity must be conducted in accordance with any conditions specified as part of the consent.

Setting	Specific Controlling Provisions for Removal of Tissue
Diagnosis & Therapy 	1. Where tissue is removed for a therapeutic or diagnostic purpose but *will also be used for research purposes*, appropriate consent must be obtained for the research purposes *in addition to* the consent obtained for the therapeutic or diagnostic procedure. 2. Cannot store, supply or use the tissue for research or any other purpose unless the medical practitioner or the healthcare institution has completed all the necessary therapeutic or diagnostic procedures.
Research 	Where the tissue is to be removed for a research purpose, appropriate consent must be obtained for the tissue to be removed from the donor. • Where the donor is an adult, consent is obtained from the donor. • Where the donor is a minor with sufficient understanding and intelligence, consent is obtained from both the minor and at least one adult parent or guardian.

Sections 6, 12 & 14

APPROPRIATE CONSENT FOR TAKING OF HUMAN TISSUE

Withdrawal of consent:

Consent may be withdrawn at any time by the subject or his proxy if :

1. the tissue is individually-identifiable and has not been used for the research; or
2. the tissue is individually-identifiable and has been used for the research but it is practicable to discontinue further use of the tissue in research

N.B. Withdrawal does not affect any research info or data obtained before the consent is withdrawn

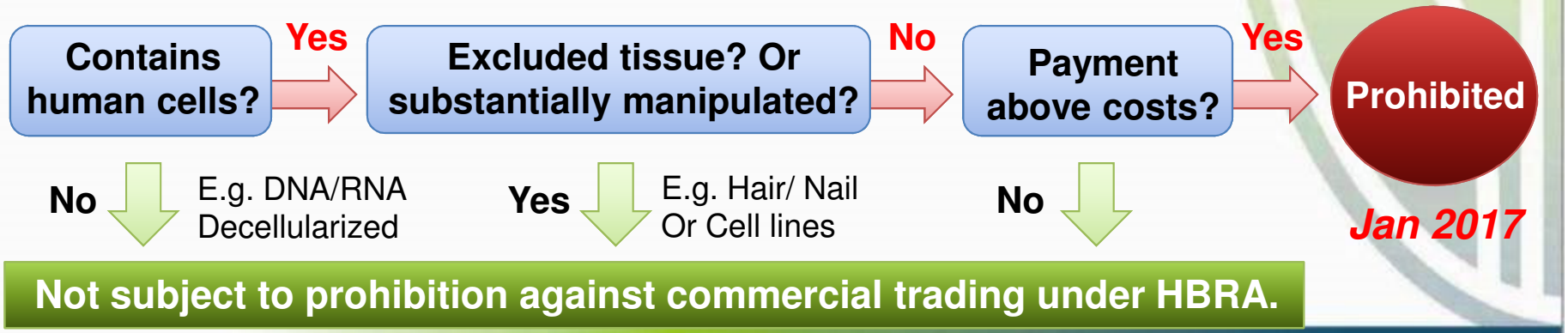
Consent Form

- ✓ Specific/general research?
- ✓ Tissue for other purposes?
- ✓ Proposed area of research?
- ✓ Compensation to injury
- ✓ Right to withdraw consent
- ✓ ID info for future research?
- ✓ Re-identified for IF?
- ✓ Renunciation of rights & IP
- ✓ Use in individually-identifiable form?
- ✓ Use in restricted research?
- ✓ Exported overseas?

Sections 32, 33 *To come into force in Jan 2017*

PROHIBITION AGAINST COMMERCIAL TRADING

- Commercial trading (i.e. buying and selling) of "human tissue" is generally **prohibited**.
- However….
  - buying and selling of tissue derivatives and tissue products, which are not considered to be "human tissue", is **permissible**
    - e.g. substantially manipulated tissue, culture-expanded cell lines
  - obtaining "human tissue" from non-commercial sources, with payment for costs or expenses (processing, storage, transport), is **permissible** in principle
    - e.g. not-for-profit tissue sharing/exchange networks/programmes



WAIVER OF CONSENT FOR 'HISTORICAL' DATA NEW!

For health information collected before a particular date (e.g. before 1 January 2017)

- **IRB may waive the requirement to obtain consent** for the research use of individually-identifiable health information that had already been collected in the past.

Conditions of Waiver: ***(To be prescribed under HBRA)***

1. the research cannot reasonably be accomplished without using the health information in an individually-identifiable form;
2. contacting the patients to obtain consent will involve a disproportionate use of effort and resources relative to the study requirements;
3. the use of the individually-identifiable health information involves no more than minimal risk to the research subject; and
4. the waiver will not otherwise adversely affect the rights and welfare of the research subject.

Note:

1. Waiver would not be applicable to individually-identifiable health information collected after the prescribed date. (A different set of conditions apply)
2. The research institution (RI) will continue to be responsible and answerable to the research subjects for the use of their individually-identifiable health information.
3. Research subjects would retain their right to subsequently withdraw from participation should they become aware that their health information is being used.

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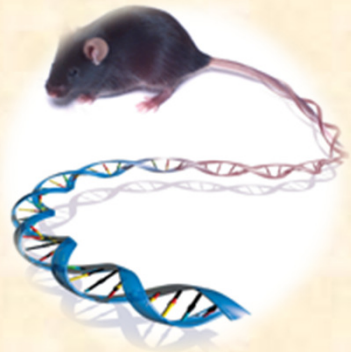
SINGAPORE

Thank You

hbr_enquiries@moh.gov.sg

SCOPE OF REGULATED RESEARCH

- Some human-animal combination research fall outside the scope

Types of HAC	How They Are Created	Not Necessary to Regulate
Animal chimeras 	By introducing human tissues or cells, other than human stem cells, into an animal.	Human cells are routinely introduced into animals to create various disease models. These entities are unlikely to generate controversial HACs, as the risk of humanisation is low.
Transgenic animals 	By introducing human genes into an animal embryo.	Transgenic animals are widely used in research, and not thought to raise any new ethical difficulties. (*BAC Report 2010*)

Sections 34, 35, 36

DUTIES AND RESPONSIBILITIES OF TISSUE BANK

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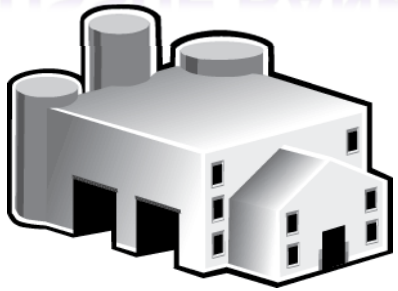
1. ✓ Notify MOH before the commencement of any 'tissue banking activity'
✓ Annual declaration of compliance
✓ Report Serious Adverse Events

2. ✓ Exercise supervision & control over its tissue banking activities, including formulating policies & standards

3. 

✓Appoint **PIC** to ensure compliance with regulatory requirements

TISSUE BANK



4. 

✓System of tracking consent

5. 

Release of tissue for research **(local)**

Individually identifiable tissue
✓ Tissue Bank must sight IRB approval

De-identified tissue
✓ Tissue Bank must sight IRB approval **OR** scientific review (e.g. public grant)

Import or Export for research **(over-seas)**

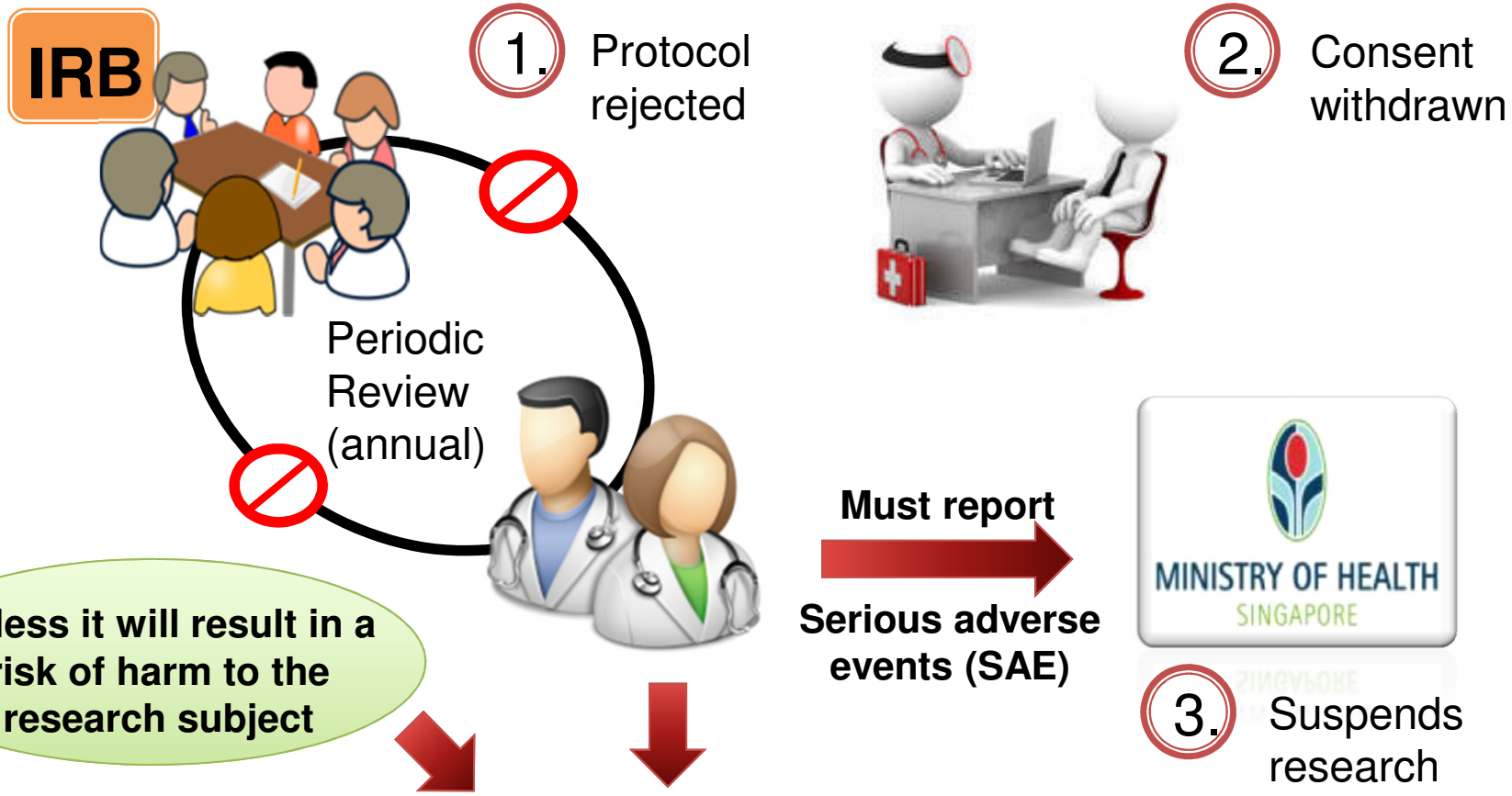
Export of tissue for research:
✓ Consent must be obtained
✓ Letter of undertaking by receiving party (to be prescribed)

Import of tissue for research:
✓ Consent given in accordance with the legal/ethical req. of that place

Section 22

DUTIES OF RESEARCHERS

~After protocol has been approved, research must stop if...



Research discontinued!

Sections 6, 12 & 14

APPROPRIATE CONSENT FOR HBR

General rule-

"Appropriate consent" must be obtained:

1. In **writing**;
2. From the subject **personally**;
3. After subject is **given full explanation** on research & expected involvement
4. **Prior** to subject involvement (intervention OR use of ID material OR ID health info)

Withdrawal of consent:
Consent may be withdrawn at any time by the subject or his proxy

N.B. Withdrawal does not affect any research info or data obtained before the consent is withdrawn

Consent Form

- ✓ Purpose of research
- ✓ Risks & likely benefits
- ✓ Alternative treatment
- ✓ Compensation for injury
- ✓ Right to withdraw consent
- ✓ Biomaterial for future use?
- ✓ Contacted for re-consent?
- ✓ ID info for future research?
- ✓ Re-identified for IF?

Sections 15, 16

APPOINTMENT OF IRB

RI-1

RI-2

Appoint

IRB-A

RI can appoint and maintain <u>more than</u> 1 IRB.

Appoint

IRB-B

RI-1 and RI-2 can have understanding to appoint **same/similar** group of individuals to be on their respective IRBs. (**N.B. esp in multi-centred trials**)

RIs responsible for providing admin support to ensure effective functioning of its IRB(s).

Key Principles :

1. Each RI must appoint its own IRB (for accountability).
2. 'Stand-alone' IRBs 'for hire' will not be recognised.
3. The same group of IRB members may be appointed by more than one RI.

Sections 18, 19

COMPOSITION, QUORUM & PROCEEDINGS

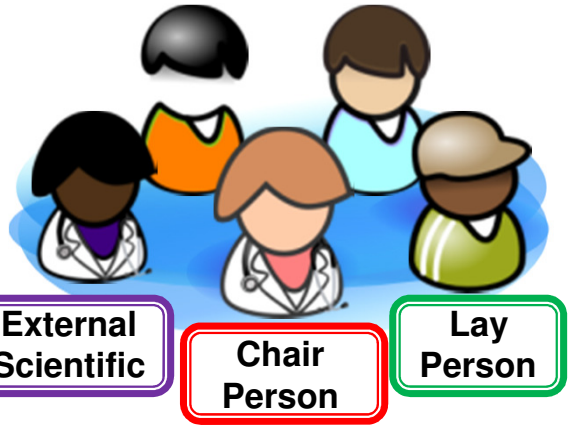
Composition

- Min 5 members for quorum
- At least 1 external scientific person and 1 (external) lay person
- Chairman must be registered medical practitioner

Decision making

- Approval by simple majority
- If tie = protocol rejected
- Conflicted member cannot vote, but may sit in to provide inputs and other information the board may require

Quorum



May advise but cannot vote.

Conflict of interest

- Members of IRB must declare at every meeting the nature & extent of all or potential conflicts in relation to a matter under consideration

Disqualification

- Undischarged bankrupt
- Convicted of an offence under this Act/ those involving fraud & moral turpitude
- Medically unfit to perform his duties

Section 17

FUNCTIONS & DUTIES OF IRB

IRB

1. To carry out ethics review of HBR proposal

2. Review the suitability and adequacy of the system of oversight (protocol specific)

RI

3.

Ensure adequate data & safety monitoring

4. Assess suitability of research site

5. Assess qualification of researcher

6. Assess capability of minor to give consent

Scientifically necessary?
Ethically appropriate?

Section 17

TYPES OF IRB REVIEW

Expedited

- For projects that pose minimal or remote risk.
- Chairman or authorised IRB member(s) to decide whether to expedite.

Full Review

- For projects that :
  1. pose more than "minimal risk"; or
  2. are "sensitive" and need deliberation of special ethical concerns.

Exempted

- For projects with no likelihood of harm to research subjects.
- Chairman or authorised IRB member(s) to decide whether to exempt.

Sections 20, 21

APPLICATION TO IRB FOR REVIEW & APPEAL

2. Direct the 1st Board to reconsider

IRB1

IRB1 rejects research proposal

With written justification

Appeal within 30 days

1. Dismiss appeal

RI

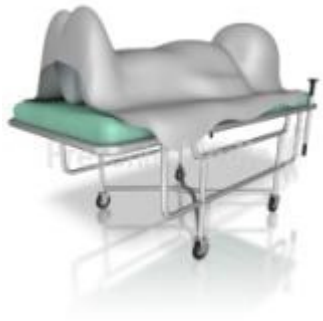
IRB2

No appeal against decision

3. Direct the 2nd Board for a 2nd Review

Sections 7, 9, 11

PROXY CONSENT FOR DECEASED & MENTALLY INCAPACITATED ADULTS

Group	Condition	Additional Requirement
	Those who are deceased. Cannot participate in restricted research	**Consent hierarchy**: Spouse → adult son/daughter → either parent/ guardian → bro/sis → administrator/executor → person authorised to dispose of the body of the deceased person *MTERA: Medical (Therapy, Education & Research) Act*
	Those who lack capacity (Mental Capacity Act) to give consent. Cannot participate in restricted research	1. Donee/deputy, → **MTERA** → *named person*. 2. Research of comparable effectiveness cannot be carried out without the participation of this class of persons. 3. **Tissue removal: primary purpose must be for treatment (therapy/diagnosis)**

MTERA

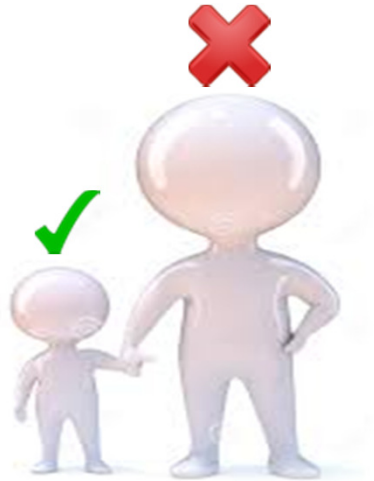
Section 8, 10

CONSENT FOR RESEARCH INVOLVING MINORS

Minor class	Condition	Additional Requirement
	Those **with** sufficient understanding and intelligence to understand the proposed research	**Both** the minor and at least one adult parent/guardian to give consent
	Those **w/o** sufficient understanding and intelligence to understand the proposed research	1. At least **one** adult parent/ guardian to give consent. 2. Research of comparable effectiveness cannot be carried out without the participation of this class of persons 3. **Tissue removal: primary purpose must be for treatment**
	Those who **lack** mental capacity (e.g. Down syndrome)	Cannot participate in restricted research

Section 13

WAIVER OF REQUIREMENT TO OBTAIN PARENTAL CONSENT

Waiver for obtaining parental consent	Conditions for Waiver
 **Research involving minors with sufficient understanding and intelligence**	**IRB must be satisfied that-** 1. The research involves no more than minimal risk to the research subjects; 2. Waiver of parental consent will not adversely affect the rights and welfare of the research subjects; 3. Research may not be practicably carried out unless there is such a waiver, **AND** 4. Research is designed for conditions for a research subject population for which parental consent is not a reasonable requirement to protect the research subjects, and an appropriate mechanism for protecting the minor is substituted; **OR** 5. Research is of such a private and sensitive nature that it is not reasonable to require permission

SCHEDULE V Part 3

WAIVER OF REQUIREMENT TO OBTAIN APPROPRIATE CONSENT FOR EMERGENCY RESEARCH

Waiver for obtaining appropriate consent	Conditions for Waiver
 Emergency Research	**IRB must be satisfied that-** 1. The research subjects are in a life-threatening situation & there is no professionally accepted standard of treatment 2. Research may not be carried out unless there is a waiver 3. Collection of valid scientific evidence is necessary to determine safety & effectiveness of a particular treatment 4. There is prospect of direct benefit to the research subjects 5. Obtaining appropriate consent is not feasible because the subjects will not have capacity and there will be no proxy available to give appropriate consent

Additional Safeguards:

1. Provision is made for a medical practitioner who is registered under the Medical Registration Act (Cap.174) as a specialist in the specialty relating to the research who is not involved in the research as a researcher or supervisor to certify, prior to the enrolment of the subject to the best of the specialist's knowledge that the conditions above are complied with. **AND**
2. The research subject **OR** proxy is to be informed as soon as is practicable after she gains capacity of the subject's participation in the research and given an opportunity to withdraw.

Section 37

TISSUE REMOVAL INVOLVING MINORS & ADULTS WHO LACK MENTAL CAPACITY

Group	Consent	Additional Restriction
Minors who (i) lack sufficient understanding and intelligence, or (ii) lack mental capacity 	Consent is obtained from at least one adult parent or guardian. Not allowed for restricted research	The tissue is removed primarily for a therapeutic or diagnostic purpose.
Adults who lack mental capacity 	Consent is obtained from a proxy according to specified hierarchy i.e. donee/deputy (MCA), MTERA proxies. Not allowed for restricted research	The tissue is removed primarily for a therapeutic or diagnostic purpose.

IRB may waive the additional restriction if the board is satisfied that :

a) the removal of tissue involves no more than minimal risk or discomfort; **AND**

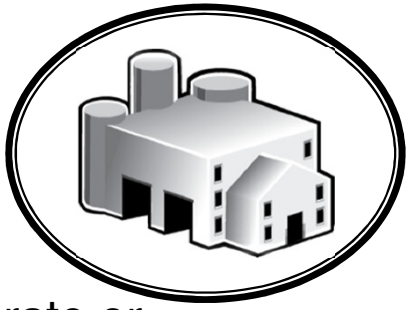
b) the proposed area of research cannot be carried out without the use of the tissue from such class of persons.

Schedule 5 – Part 1 & 2

WAIVER OF APPROPRIATE CONSENT

Waiver for obtaining written consent	Conditions for Waiver
	**IRB must be satisfied that –** 1. The research or use of the human tissue involves no more than minimal risk to the research subject or donor and involves no procedures for which written consent is ordinarily required outside of a research context; **OR** 2. The only record linking the subject/donor and the research/tissue is the consent form and the principal risk to the subject/donor is the potential harm resulting from unauthorised disclosure of confidential information.
Waiver for obtaining appropriate consent	**Conditions for Waiver**
 **Individually identifiable Biological Material & Health Information**	**IRB must be satisfied that –** 1. The research may not be practicably carried out unless there is a waiver; 2. The research involves no more than minimal risk to subject; 3. The waiver will not adversely affect the rights & welfare of the research subject or donor; **AND** 4. The research would reasonably be considered to contribute to the greater public good.

REGULATION OF TISSUE BANKS



- Some parties may be regarded as "tissue banks"

"Tissue bank"

"…means an individual or a body of persons, whether corporate or unicorporate, or other organisation, that carries on or conducts any **tissue banking activity**…"

"…**excludes** an individual, a body of persons or an organisation that conducts any tissue banking activity solely for the purposes of the person's or organisation's own human biomedical research approved or exempted from review by an IRB."

"Tissue banking activity"

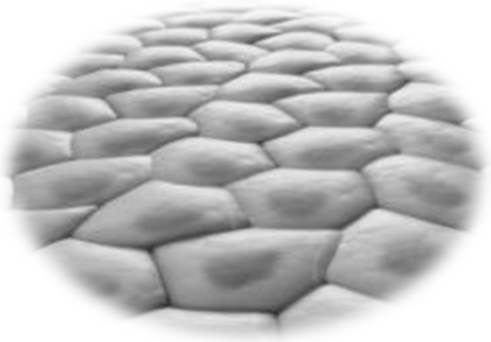
"…means a structured and organised activity involving human tissue for the purposes of facilitating current or future research or for public health or epidemiological purposes or any combination of such purposes, including any of the following activities :

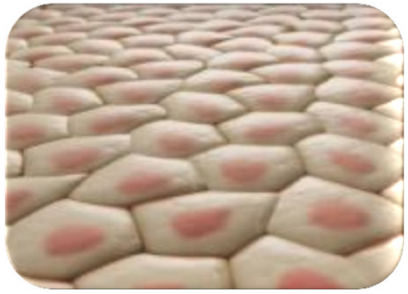
(a) the collection, storage, procurement or importation of human tissue;

(b) the supply, provision or export of human tissue."

Section 64, 37

LEGACY TISSUES & IMPORTED TISSUES

Legacy tissues	Exception to facilitate the use of legacy tissues
	"Legacy human biological material" – which had been removed from the donor's body and rendered non-identifiable, prior to the Act coming into force. Exceptions will be made to allow such non-identifiable legacy tissues to be used in research *without* appropriate consent.

Imported tissues	Exception to facilitate the use of imported tissues
	For imported tissues, it shall be sufficient compliance if there is documentary evidence that consent has been obtained in accordance with the legal or ethical requirements of the place where the tissue came from.