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Overview of the Human Biomedical Research Framework

Updated August 2021

HBRA was implemented in phases – now fully activated

Activated on 1 Jul 2016

Phase 1

Administrative provision

Activated on 1 Jan 2017

Phase 2

Prohibition against commercial tissue trading

Activated on 1 Nov 2017

Phase 3

HBR Framework

Regulation of human biomedical research

- Functions and duties of IRB (S17)
- Functions and duties of RI (S23)
- Approval and conduct of restricted research (S31)
- Amendment to Third, Fourth and Fifth Schedules of the HBRA

Activated on 1 Nov 2019

Phase 4

HTF Framework

Regulation of research tissue banking

- *Duties of tissue bank (S34-36) and other controls to be prescribed*
- *Restrictions on activities relating to human tissue (S37)*
- *Compelling person to donate tissue (S38)*
- *Restriction on disclosure of information on tissue donor (S39)*
- *Savings & transitional provisions for legacy human biological material (S64)*

Core objectives:

- Ensure the safety and welfare of research subjects and tissue donors
- Regulate certain 'sensitive' research
- Prevent commercial trading of human tissue

What is considered ‘HBR’ under the HBRA?

Human biomedical research (HBR) covers 2 broad areas:

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

and

Certain types of ‘sensitive’ embryological and stem cell research, as per section 3(3)

What is considered 'HBR' under the HBRA?

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

Intended Purposes

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,

Methodologies

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 human biological material** obtained from the human body; **or**

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

What is considered ‘HBR’ under the HBRA?

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).”

HBR that is prohibited or restricted under the HBRA

- In addition,
  - some HBR are 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 are classified as "prohibited human biomedical research"
    - specified in the Third Schedule.
    - not allowed to be conducted at all, per section 30.

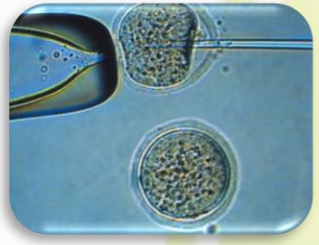
HBR that is prohibited or restricted under the HBRA

- Overview of “restricted” HBR as specified in the Fourth Schedule and “prohibited” research as specified in the Third Schedule

Human Embryo

Human Egg

Cytoplasmic Hybrid



Animal Chimeras

PROHIBITED

Development beyond 14 days

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

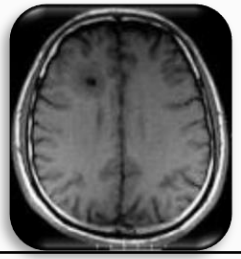
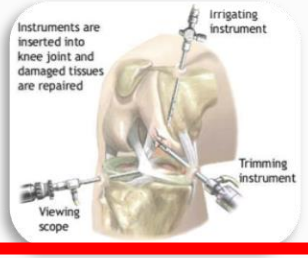
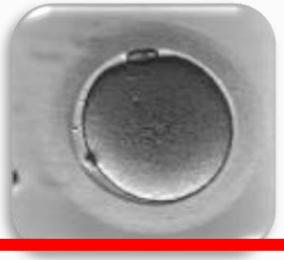
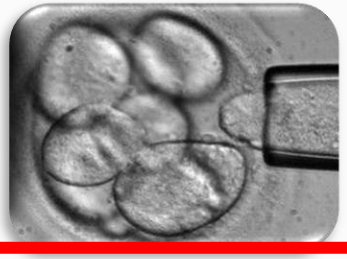
PROHIBITED

Breeding

Adult animal

Examples of ‘HBR’ under the HBRA

Research involving the following:

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**

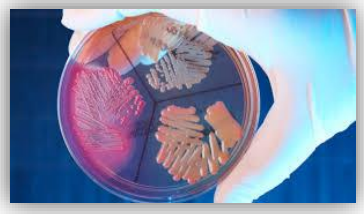
Restricted Human Biomedical Research

Studies that are not regulated under the HBR Framework

Service Evaluation
-Designed and conducted solely to define or judge current care

Clinical Audit
-Designed and conducted to produce information to inform delivery of best care

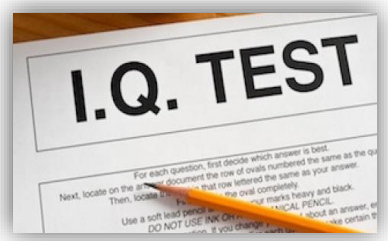
Surveillance
-Designed to guide public health policies, programmes and actions to prevent and control the diseases.



Outbreak Investigation
-Designed to determine the source of the outbreak, and actions are to prevent and control transmission of disease. Findings may also guide public health policies.

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

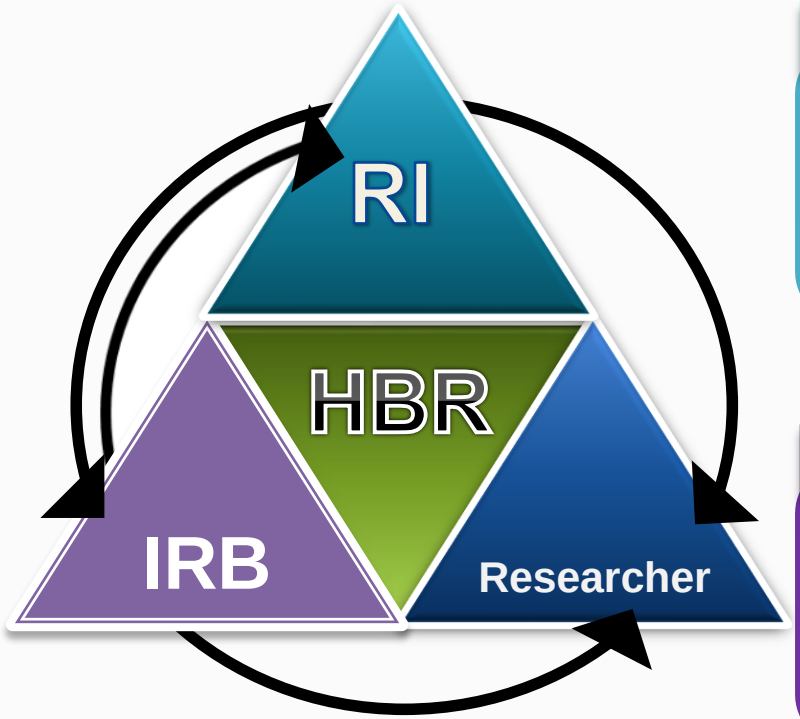
Normal psychological responses and behaviours



Measurement of human intelligence

Public health research permitted and/or required under other laws

Ensuring proper research governance through interlocking accountabilities



Formalizing of existing research governance framework between the 3 main entities

Research Institution (RI)

Overarching entity responsible for the HBR conducted under its supervision & control. Must appoint and support the IRB amongst other key responsibilities.

***RI is overall accountable.**

Institutional Review Board (IRB)

Provides independent and objective ethics review of research projects, assess qualification of researcher and suitability of research sites, amongst other responsibilities.

Researcher

Research must always be conducted under the supervision and control of a RI. Must ensure that research participation is voluntary and ethics approval has been granted.

What does it mean if your research is HBR?

2. Protocol reviewed and approved or exempted from review

IRB

3. Appropriate consent obtained in accordance with Part 3 of the HBRA

1. Must come under the supervision of an RI

RI

Restricted Research

Fourth Schedule

4. Approved by MOH after review by Advisory Committee

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RESEARCH STARTS

Must meet the requirements specified in Part 5 of the HBRA

- **All amendments must be re-approved by IRB**
- **Must not deviate from the research that had been approved**
- **Must protect subject or donor confidentiality (Section 27)**

What does it mean if your research is HBR?

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

1. Approval withdrawn

IRB

Periodic Review

2. Subject withdraws consent

Must report

3. Suspends research

Serious adverse events (SAE)

Unless it will result in a risk of harm to the research subject

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Research discontinued!

Functions and 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 **30 days 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

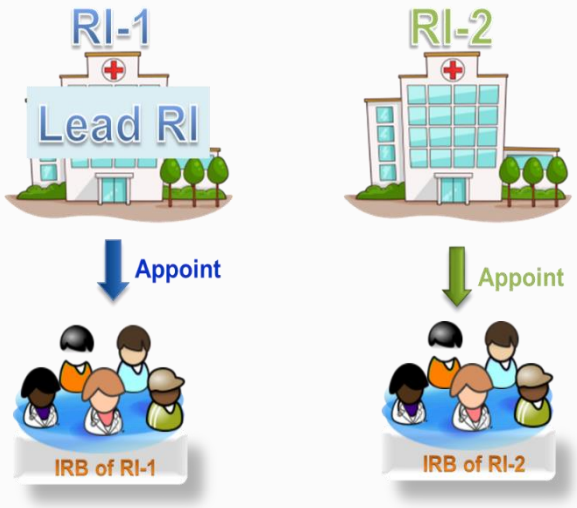
5.

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

Possible models of research collaboration

1. All institutions participate as RIs in a HBR, and one is appointed as the lead RI. A common IRB is appointed to review the HBR.

2. All institutions participate as RIs in a HBR, and one is appointed as lead RI. However each appoints its own IRB to review the HBR.



3. Only one institution participates as RI in a HBR, the other institution remains a collaborator. The RI's appointed IRB will review the HBR.

Note: Regardless of the model of collaboration, RIs and researchers should draw up a research collaborative agreement (RCA) to clearly stipulate the roles and responsibilities of each RI/party involved insofar to ensure compliance with the HBRA.

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a) Consent Requirements

Appropriate Consent Requirements under the HBRA

Does my consent fulfill the requirements of "appropriate consent" as required under the HBRA?

You would be considered to have "appropriate consent" if it was obtained

(a) in writing;

(b) from the research subject personally or their legal proxies

(c) after the information referred to in section 12 has been provided and explained to the research subject or the persons authorised to give consent on the subject's behalf under this Part, as the case may be; and

(d) in the presence of a witness. *N.B. : Witness requirement may be exempted under certain conditions:*

- **For HBR** – where the HBR is not invasive, not interventional and not restricted HBR, OR the HBR involves intervention that is no more than minimal risk to the subjects, the subject is able to read and sign the consent form, and the HBR is not restricted HBR.

Waiver of Appropriate Consent under the HBRA

What if I am not able to obtain appropriate consent from the research subjects?

You can consider applying for a waiver of appropriate consent from the IRB.

MOH's Position

- As far as possible, appropriate consent should be obtained to ensure that prospective subjects are adequately informed and given the opportunity to decide whether to participate in a HBR. **Mere inconvenience should not be the sole factor for waiver of consent.**

There are several types of waivers under the HBRA, namely:

- Waiver of written consent;
- Waiver of appropriate consent for the use of individually-identifiable health information (HI) and/or human biological material (HBM);
- Waiver of appropriate consent for emergency research; and
- Waiver of parental/guardian consent (section 13 of HBRA).

Waiver of Appropriate Consent under the HBRA – Criteria for Waiver

For Historical ID HBM/HI (*before 1 Nov 2017*)

IRB must be satisfied that –

1. The individually-identifiable human biological material was obtained or compiled before 1 November 2017;
2. The research cannot reasonably be carried out without the use of the human biological material in an individually-identifiable form;
3. The use of the individually-identifiable human biological material involves no more than minimal risk to the research subjects;
4. The waiver concerned will not otherwise adversely affect the rights & welfare of the research subject; **AND**
5. For HBM: reasonable effort has been made to re-contact the person to which the individually-identifiable human biological material relates for the purpose of obtaining his or her consent

   For HI: the process of obtaining consent from the person, to which the individually-identifiable health information relates, will involve a disproportionate amount of effort and resources relative to the research requirements.

For ID HBM/HI (*after 1 Nov 2017*)

IRB must be satisfied that –

1. The research cannot reasonably be carried out without the use of the human biological material or health information in an individually-identifiable form;
2. The process of obtaining consent from the person, to which the individually-identifiable human biological material or health information relates, will involve disproportionate amount of effort and resources relative to the research requirements;
3. The research involves no more than minimal risk to the subjects;
4. The waiver will not adversely affect the rights & welfare of the research subject or donor;
5. The research would reasonably be considered to contribute to the **greater public good (e.g. epidemiology research & population wide study – BAC report 2002)**.

E.g. of "reasonable effort": Notification to be served by mail/electronically, subjects given 30 + 30 days to respond

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b) Reporting of SAE & Contraventions

Definition of Serious Adverse Event

What is considered a Serious Adverse Event?

Any untoward medical occurrence as a result of any HBR that

i. results in or contributes to death;
ii. is life-threatening;
iii. requires in-patient hospitalisation or prolongation of existing hospitalisation;
iv. results in or contributes to persistent or significant disability or incapacity;
v. results in or contributes to a congenital anomaly or birth defect;
vi. results in the transmission of a communicable disease; or
vii. results in any misidentification or mix-up of any type of human biological material, gametes or embryo.

SAE and Contravention Reporting under the HBRA

Suspected Offence/ Contravention (SOC)

SOC resulted in harm or had potential to cause harm to any subject

RI submits all relevant information to MOH within **7 days** after knowing the event

SOC did not result in harm and did not have potential to cause harm to any subject

RI submits all relevant information to MOH in aggregate during its next declaration of compliance

Serious Adverse Event (SAE)
must be reported to the RI immediately

Death / Life Threatening

RI submits all relevant information to MOH within **7 days** after knowing the event

RI submits any additional relevant information to MOH within **8 days** after the record is made

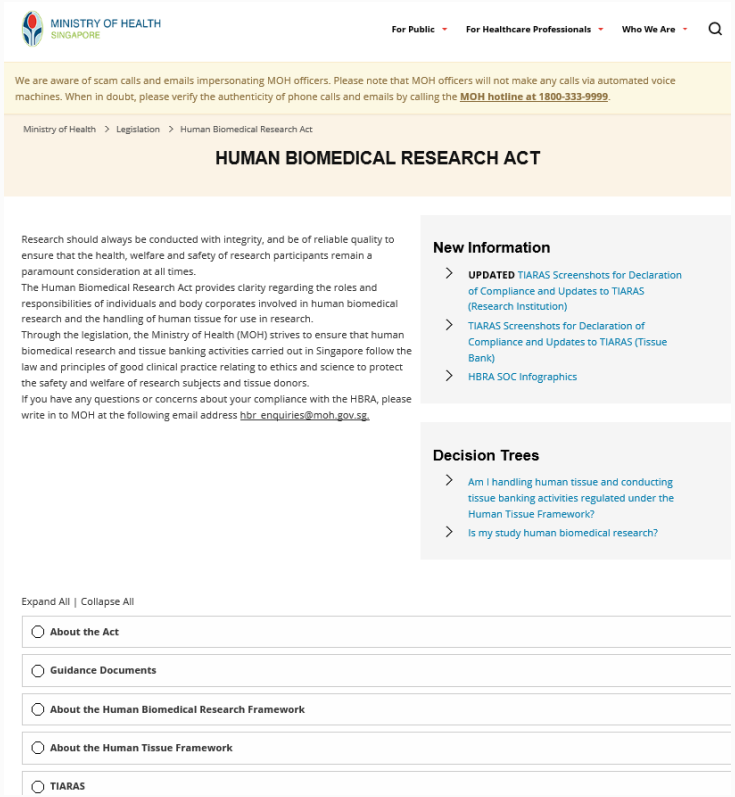
Others

RI submits all relevant information to MOH within **15 days** after knowing the event

Note: SAE and SOC reporting forms can be found on TIARAS and should be submitted to hbr_enquiries@moh.gov.sg

References and Useful Links

- HBRA and its Regulations: https://sso.agc.gov.sg/Act/HBRA2015
- MOH's website on the HBRA: https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act



<u>Contains the following useful resources and tools:</u>

- Decision tools (to help you determine whether you are conducting HBR, or whether you are regulated under HTF);
- Infographics on SAE/SOC reporting;
- Guides e.g. on prohibition against commercial trading of human tissue, a table differentiating research from other non-research activities such as service evaluation.

- TIARAS: https://elis.moh.gov.sg/tiaras/
  - Forms for reporting SAEs and SOCs are found in the "Resources/Other links" page of TIARAS.