MINISTRY OF HEALTH
SINGAPORE

Overview of Human Tissue Framework

Updated July 2021

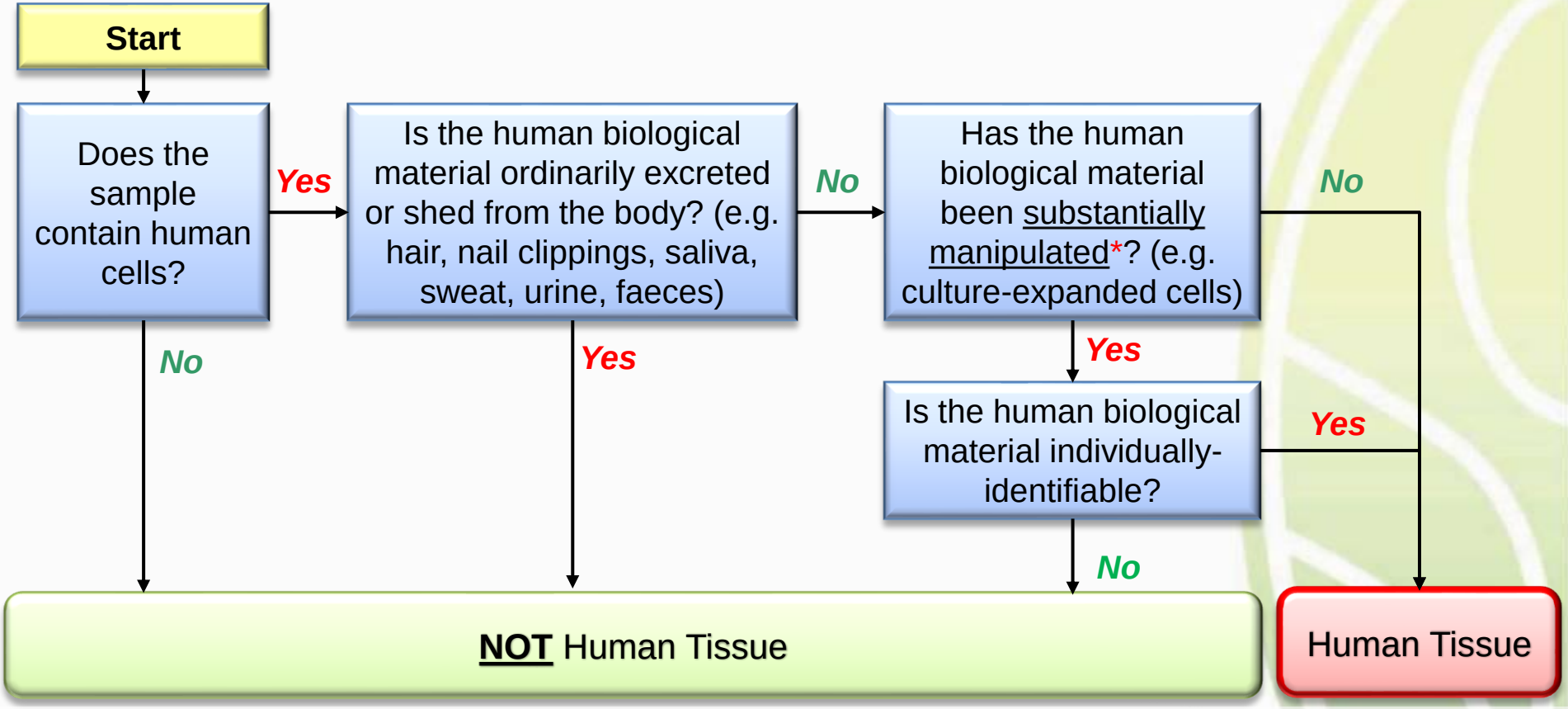
HBRA implementation plan and timelines

Human Biomedical Research Act (HBRA)

Phase 1	Phase 2	Phase 3	Phase 4
Activated on 1 Jul 2016	***Activated on 1 Jan 2017***	***Activated on 1 Nov 2017***	***Activated on 1 Nov 2019***
			
Administrative provision	Prohibition against commercial tissue trading	**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	**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)*

Definition of Human Tissue under the HBRA

What is considered human tissue (HT) under the HBRA?



N.B. A sample is considered to be substantially manipulated if it has been processed in a manner such that its functional, structural and biological characteristics are substantially manipulated as compared to the time of collection from the donor.

Processes that would not be considered to be substantial manipulation include cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, low-level irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing, cryopreservation, vitrification.

Further guidance on "substantial manipulation" can be found in the MOH Guide on Prohibition Against Commercial Trading of Human Tissue.

Definition of Tissue Bank under the HBRA

TISSUE BANK

"…means an individual or a body of persons, whether corporate or unincorporate, 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 ACTIVITIES

"… means a structured and an 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.

Refer to Annex A

Annex A: What are "Tissue Banking Activities" regulated by the HBRA?

"Incoming" activities

Storage – keeping HT in the TB premises (including temporary storage)

Collection – receiving or removing tissue (from donors) for your TB. This includes receiving tissue from other tissue banks, hospitals or researchers.

Importation – bringing in HT from overseas into Singapore

"Outgoing" activities

Supply/Provision – providing/distributing HT to other persons or entities within Singapore

Export – sending HT overseas from Singapore (includes exporting HT to overseas lab for testing for research purposes)

When is an entity not considered a TB?

I am NOT a TB when I conduct the following activities :

1. TB activities for my **own Clinical Trial (CT)** regulated under the Health Products Act (HPA) / Medicines Act (MA).
2. TB activities for my **own HBR** regulated under the HBRA. **Note**: HBRA Section 37 will still apply.
3. TB activities for my **own National Public Health Research** regulated under Section 59A of the IDA.
4. TB activities as **part of my contracted duties solely to support a CT/HBR** (e.g. CROs, processing labs). My TB activities are conducted on behalf of the sponsor/researcher/RI to support their CT/HBR as described in Points (1) & (2). The contracted activities must be clearly stated in a contractual agreement with the sponsor/researcher/RI.

Note: For activities 1 - 4, the requirements of the relevant Acts e.g. HPA, MA, IDA, HBR framework will still apply.

I am still a TB when I conduct the following activities (examples) :

A. TB activities involving **leftover tissue** from my current HBR or CT for **future research**

B. TB activities (e.g. biobanking) **beyond the objectives & endpoints** of the protocol approved by the IRB and/or regulatory agencies e.g. HSA.

C. TB activities involving **additional tissue** beyond what is approved for my HBR or CT.

D. Supply any leftover tissue from my current HBR or CT to **other researcher(s)** for research that is not my own research.

E. TB activities for pre-clinical studies (e.g. research conducted using human tissue before actual clinical trial starts).

Note: For activities A - E, the requirements of the Human Tissue Framework under the HBRA will still apply.

When is an entity considered a TB?

Scenario 1: Where researcher is considered a TB

*A researcher **intends to collect 10 ml of blood** – 5 ml of blood would be used for his/her own current HBR **while the other** 5 ml of blood would be stored for **future research studies** (i.e. collection of **additional** blood).*

The researcher would be considered to be conducting tissue banking activities not just for his/her own IRB-approved HBR and would need to be a TB or come under the supervision and control of a TB.

Scenario 2: Where researcher is not considered a TB

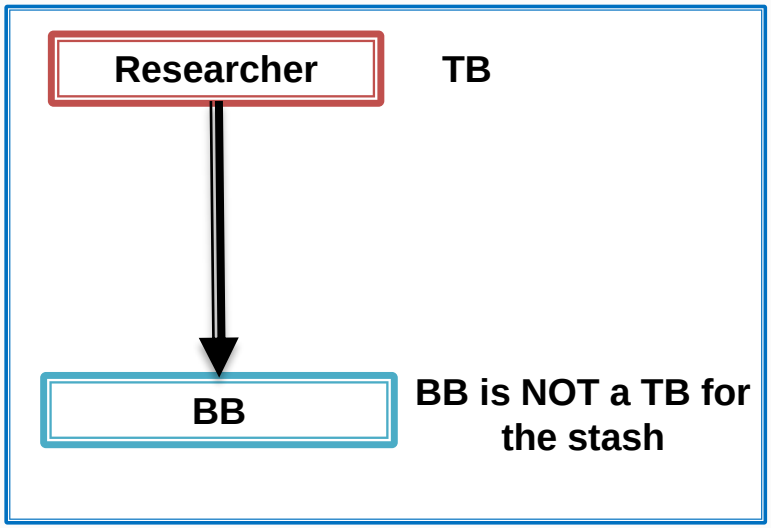
*A researcher **intends to collect 10 ml of blood** – the entire 10 ml was intended to be used in his/her own current HBR; however he/she only used 5 ml in the research and the other 5 ml was **leftover**. The researcher decides to use the leftover blood for his/her other own IRB-approved HBR.*

The researcher would be considered to be conducting tissue banking activities just for his/her own IRB-approved HBR. Hence the researcher would not need to be a TB or come under the supervision and control of a TB, until he/she decides to supply the leftover blood to other researchers.

When is an entity considered a TB?

Example 1

Researcher asks biobank (BB) to conduct tissue banking activity on his or her behalf, but researcher remains responsible for complying with the HBRA.

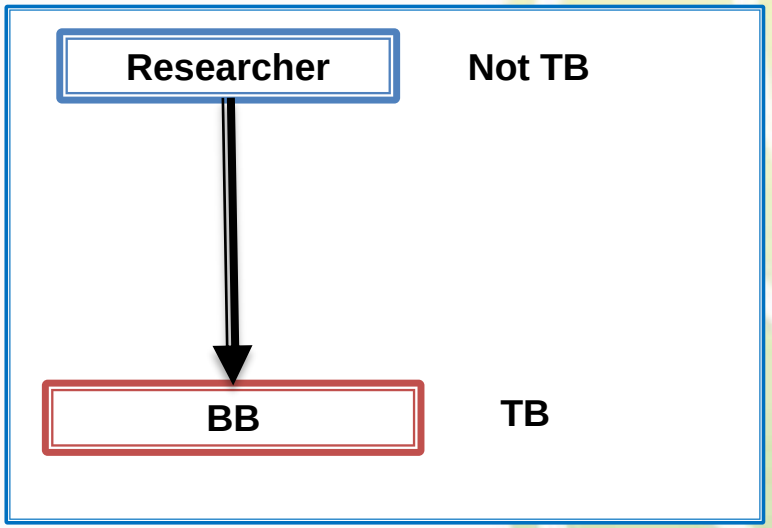


Responsibility of the researcher in ensuring compliance with the HBRA for the tissue is clearly stated in agreement between researcher and BB.

Researcher to become a TB or come under an existing TB.

Example 2

Researcher asks BB to conduct tissue banking activity on his or her behalf, but BB is responsible for complying with the HBRA.

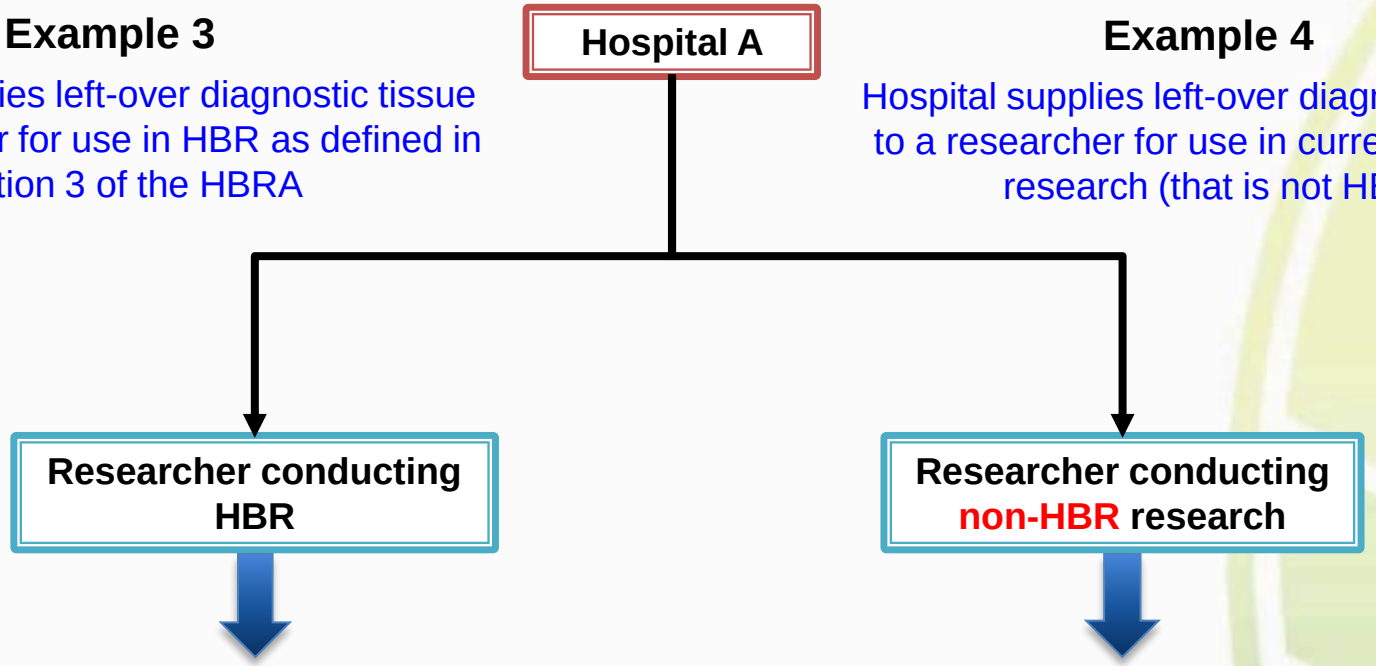


Responsibility of the BB in ensuring compliance with the HBRA for the tissue is clearly stated in agreement between researcher and BB.

When is an entity considered a TB?

Example 3

Hospital supplies left-over diagnostic tissue to a researcher for use in HBR as defined in section 3 of the HBRA



Example 4

Hospital supplies left-over diagnostic tissue to a researcher for use in current or future research (that is not HBR)

- Hospital A is a TB as it is supplying tissue
- Researcher is **excluded** from having to be a TB

- Hospital A is a TB as it is supplying tissue
- Researcher is considered a TB unless he comes under the governance of a TB.

Hospital A would need to notify MOH as a TB and would be required to ensure:

1. Consent requirements;
2. Diagnostic purposes have been completed before tissue is released.

Researcher would need to be a TB or come under the supervision and control of a TB if he is not conducting tissue banking activities for his own HBR.

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Overview of Key Requirements Under the HTF

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KEY HTF REQUIREMENTS

1. Commencement & Cessation

- ✓ Notification of operations
- ✓ PPIC
- ✓ Notification of Cessation

2. Operational requirements

- ✓ Declaration of Compliance
- ✓ Requirements before human tissue is collected, stored, supplied or exported
- ✓ Protection of confidentiality of donor's information
- ✓ Incidental Findings Policy
- ✓ Safety and welfare of donors

3. Consent Requirements

- ✓ Tracking of consent and integrity of records
- ✓ Imported tissue and legacy human biological material
- ✓ Exemption from witness requirements

4. SAE, UO & Contravention

- ✓ Notification of SAE to TB
- ✓ Notification by recipient of HT to TB
- ✓ Notification to Directo by TB

5. For Transplantation Research

- ✓ Documentation
- ✓ Additional requirements before tissue is released, supplied or exported
- ✓ Management of Tissue Contamination
- ✓ Quality and Safety Management System

Note: Please refer to Part 3 & 6 of the HBRA and HBR(Tissue Banking) Regulations 2019 for the full set of HTF requirements.

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1. Commencement & Cessation of Tissue Banking Operations

Commencement and Cessation of Tissue Banking Operations

Notification of Operation

Existing Tissue Bank	New Tissue Bank
Tissue bank that has started any tissue banking activity before 1 November 2019*	Tissue bank that has **not** started any tissue banking activity before 1 November 2019

The notification required to be submitted by a tissue bank must be in the applicable form set out at the relevant website (TIARAS) and must contain all of the following information:

a) the name of the tissue bank and the address, telephone number and email address at which that tissue bank may be contacted;

b) such other information as may be required or specified in the form set out on that website (TIARAS).

Submit the notification **no later than 30 days** after 1 November 2019	Submit the notification **no later than 30 days** before the start of its first tissue banking activity

**activation date of the Human Tissue Framework*

Commencement and Cessation of Tissue Banking Operations

Notification of cessation of tissue bank's operations

A tissue bank must notify MOH of its intention to cease operating as a tissue bank as soon as possible (not less than 30 days before the cessation of operation). The notification will include:

a) disposal plan for the human tissue samples and information related to such tissue;
b) date and reason for cessation
c) where the plan involves the transfer of the human tissue or information related to the tissue to another tissue bank, it should also include —
    i. name, address and contact particulars of the receiving bank; and
    ii. documentary evidence provided by the receiving bank that the receiving bank will ensure that the intended use of the tissue is in accordance with any restrictions specified by the donors during consent-taking;
d) such other information as as the Director may in any particular case require.

Principal Person-in-Charge (PPIC)

PPIC

Every tissue bank must designate a PPIC who is principally responsible for the management and control of any type of business or tissue banking activities of the tissue bank in Singapore.

The PPIC must fulfil the following requirements:

- ✓ is ordinarily resident in Singapore;
- ✓ is in the direct employment of, or acting for or by arrangement with, the tissue bank;
- ✓ has the authority to ensure that the tissue bank complies with the Act and these Regulations; and
- ✓ is suitably qualified to perform the duties of a person in charge.

Additionally, for a tissue bank that stores or supplies tissue for transplantational research, the PPIC must be a **medical practitioner**.

The PPIC must at all reasonable times be **contactable** for the purposes of the duties and functions of the tissue bank under the HBRA and its regulations.

All TB

Declaration of Compliance

Declaration of Compliance

The PPIC of the tissue bank is required to submit an annual declaration of compliance for all tissue banking activities conducted under the supervision and control of the tissue bank. The format of the annual declaration of compliance can be found in the First Schedule of the Tissue Banking Regulations 2019.

The declaration of compliance must be made in writing and submitted to the Director on **a date between 1 March and 18 April (both dates inclusive) of every year**. (Same as declaration of compliance period for RIs)

Fees to be paid

Notification of tissue bank to MOH: $1000 (one-time payment)

When tissue bank that stores or supplies tissue for the purpose of use in research involving human tissue transplantation declares compliance:

(a) First site: $4000
(b) For each additional site: $500

A tissue bank that does not store or supply tissue for human tissue transplantation will pay the following when declaring compliance annually:

(a) For the first site: $1000
(b) For each additional site: $500

A tissue bank satellite site refers to the locality where tissue is stored primarily for the purpose of onward supply of the tissue for use in research. Where tissue is stored at 2 or more premises located within the same building (bearing the same postal code in each premises' address) and under the supervision and control of a single tissue bank, these premises are counted as a single site.

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2. Consent Requirements

Appropriate Consent Requirements for Donation of Human Tissue

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 tissue donor personally or their legal proxies;

(c) after the information referred to in section 12(2) has been provided and explained to the tissue donor or the persons authorised to give consent on the donor's behalf under this Part, as the case may be; and

(d) in the presence of a witness (N.B.: Witness is not required where only leftover diagnostic tissue is used, or where the tissue removal is of no more than minimal risk and the donor is able to read and sign the consent form; research must not be restricted HBR).

Appropriate Consent Requirements

Tracking of Consent and Integrity of Records

A tissue bank must establish a system to accurately track donors' consent in relation to each tissue under the supervision and control of the tissue bank and ensure the integrity of records of the consent and other information relating to the donor.

- Documentary evidence of written consent for **each HT sample** should be maintained e.g. signed consent form or redacted consent forms (i.e. individually-identifiable information replaced with subject/donor code)

Imported Tissue

There must be documentary evidence e.g. declaration in Material Transfer Agreement or Tissue Requisition forms etc., that consent has been obtained in accordance with the legal or ethical requirements of the place where the tissue is imported from.

- Documentary evidence for multiple HT samples can be consolidated in a single document for batch import of HT samples into Singapore.

All TB

Appropriate Consent Requirements – use of human tissue in research

Exemption from need for appropriate consent if tissue collected before 1 November 2019

Sections 12 and 37 of the Act do not apply in relation to the storage, supply and use of tissue in research where—

(1) The tissue was removed from a human body any time before 1 November 2019;

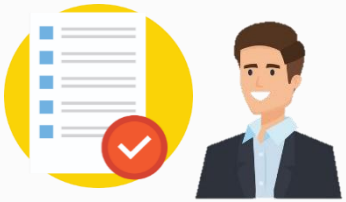
(2) There is documentary evidence indicating that relevant consent has been obtained in writing, after the minimal set of "core" information as follows has been provided and explained:

- 12(2)(a) specific research purpose for which the tissue is intended to be used, if this information is available, otherwise, the purpose may be stated as for general research;
- 12(2)(f) the donor's right to withdraw his or her consent and the limitations of such withdrawal; and
- 12(2)(i) the extent to which donor records will be kept confidential.

(3) The relevant consent was not withdrawn any time before 1 November 2019.

All TB

Appropriate Consent Requirements – use of human tissue in research



Exemption of witness requirement when obtaining appropriate consent from tissue donor

The requirement for a witness to be present during appropriate consent may be exempted in the following two scenarios:

Scenario 1

The tissue:
(a) is removed primarily for a therapeutic or diagnostic purpose; and
(b) is not to be used for restricted human biomedical research.

Scenario 2

(a) tissue removal involves no more than minimal risk to tissue donor;
(b) tissue donor is able to read and sign the appropriate consent form; and
(c) appropriate consent is not for the purpose of restricted human biomedical research.

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3. Operational Requirements

Operational Requirements

Requirements before individually-identifiable tissue may be supplied to any person for use in research

Before any tissue bank can supply **individually-identifiable tissue** for use in research (excluding export), the tissue bank must ensure that:

IRB Approval

- An institutional review board (IRB) has approved the proposed research that the tissue would be used for; **and**

LOU

- **Documentary evidence** is provided by the receiving party that the receiving party will ensure that the intended use of the tissue is in accordance with any restrictions/conditions of the donors' appropriate consent.

Before any tissue bank can export any **individually-identifiable tissue** is to be exported or removed from Singapore, there must be:

- Appropriate consent has been obtained from the donor for the export or removal, as the case may be; **and**

LOU

- **Documentary evidence** is provided by the receiving party that the receiving party will ensure that the intended use of the tissue is in accordance with any restrictions/conditions of the donors' appropriate consent.

Operational Requirements

Requirements before non-identifiable tissue may be supplied to any person for use in research

Before any tissue bank can supply **non-identifiable** tissue for use in research (excluding exporting), the tissue bank must ensure that:

IRB Approval

An institutional review board has approved the proposed research that the tissue would be used for;

OR

Scientific Merit

The tissue bank is satisfied that there is scientific merit for the proposed research.

and

There is documentary evidence provided by the receiving party that the receiving party will ensure that the intended use of the tissue is in accordance with any restrictions/conditions of the donors' appropriate consent.

De-identified tissue may be exported even if consent had not been obtained for its export from the tissue donor. However, if the donor had stipulated that he/she did not wish for his/her tissue to be exported, his/her wishes should be respected.

Operational Requirements

Protection of confidentiality of donor's information

A tissue bank must establish a system comprising such reasonable measures as may be necessary to protect the confidentiality of information relating to the donor of each tissue under the supervision and control of the tissue bank and to maintain the donor's privacy.

Policy on Incidental Findings (IF)

A tissue bank must formulate a policy on whether or not the tissue donor should be re-identified and informed in the case of an incidental finding in relation to a tissue, and this policy must be communicated to all donors and recipients of every tissue received by the TB from the date that the HTF is activated.

If the TB's policy provides for the donor to be re-identified and informed in the case of an IF, the donors' wishes in this regard (i.e. whether they had consented to be re-identified and informed, or not) should be communicated to the recipient as well.

Safety and Welfare of Donors

Safety and welfare of donors

A tissue bank involved in the removal of tissue from tissue donors for use in research, must establish a system to ensure the safety and welfare of the tissue donors.

The system must at the minimum consider the following in relation to the tissue donor:

The qualifications of and training to be received by the personnel involved in the removal of tissue;

The measures to prevent or control the spread of any communicable disease which is or may be due to the contamination or infection of any tissue;

The management of quality control and maintenance of instruments and equipment used for the removal of tissue.

Operational Requirements

Removal of Tissue from Vulnerable Persons

1. **No person may remove any HT** from any of the persons listed below unless the removal of the HT was **primarily for a therapeutic or diagnostic purpose:**

    a. Adult or minor^ who lacks mental capacity;

    b. Minor^ who lacks sufficient understanding and intelligence to understand what is proposed in the **HT donation** procedure.

2. IRB may waive the above requirement if the board is satisfied that:

    a. The removal involves no more than minimal risk to that person; and

    b. There are reasonable grounds to believe that the proposed areas of research cannot be carried out without the use of the tissue from the class of persons involved.

3. The basis for the IRB waiver should be clearly documented e.g. IRB minutes of meeting, IRB approval letter etc.

^ *below 21 years old and has never been married*

Operational Requirements

Requirements for storage, supply and use of leftover therapeutic / diagnostic tissue

Before leftover therapeutic or diagnostic samples may be stored, supplied or used for research, there should be documentary evidence from the medical practitioner or healthcare institution responsible for the medical treatment of the donor that the HT is no longer needed for therapeutic or diagnostic purposes.

Legacy Human Biological Material (HBM)

The requirements of the HBRA do not apply to legacy HBM which had been removed from the donor's body **and** rendered non-identifiable prior to 1 November 2019, except:

(1) Section 30 on prohibited human biomedical research;
(2) Section 31 on restricted human biomedical research;
(3) Section 32 on prohibition of commercial trading of human tissue; and
(4) Section 33 on prohibition of advertisements relating to commercial trading of human tissue.

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4. Reporting of SAE & Contraventions

All TB

SAE and SOC Reporting by TBs

Suspected Offence or Contravention (SOC)

1. For SOCs which did not cause harm **AND** had no potential to cause harm

-> TB to manage these SOCs institutionally and report such SOCs during the **annual** declaration of compliance

2. For all other SOCs which had caused harm **OR** had the potential to cause harm

-> TB to report these SOCs to MOH within **7 calendar days** after being made aware of the SOCs

More information can be found in the HBRA SOC infographics uploaded on the MOH's HBRA webpage.

(1) Serious Adverse Events (SAE); or
(2) Untoward Occurrences (UO)
must be reported to the TB immediately
Refer to next slide for definition of SAE & UO

Death / Life Threatening

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

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

Other SAEs or UOs

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

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

SAE and Contravention Reporting by TBs

Notification of Serious Adverse Event and untoward occurrence

(A) What is considered a Serious Adverse Event?

Any occurrence associated with the procurement, testing, processing, storage or distribution of **human tissue (including gametes or embryos) intended for human application** which:
(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 the transmission of a communicable disease; or
(vi) results in any misidentification or mix-up of any type of tissue, gametes or embryo.

(B) What is considered an Untoward Occurrence?

Any occurrence associated with the **removal of human tissue primarily for research** 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 the transmission of a communicable disease;
(vi) results in any misidentification or mix-up of any type of tissue, gametes or embryo; or
(vii) results in or contributes to a congenital anomaly or birth defect.

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5. Additional Requirements for Tissue Banks Supporting Transplantation Research

Additional Requirements for TBs supporting Transplant Research

[Note: These requirements are for Transplantational Research TB: stores or supplies tissues for the purpose of use in research involving **human tissue transplantation**[1]**.**]

Documentation

A tissue bank must maintain a record containing a detailed description of the condition of each tissue under the supervision and control of the tissue bank, including any observed tissue abnormalities or imperfections.

Notification by recipient of Human Tissue

A tissue bank must ensure that the recipient of human tissue stored or supplied by the bank is informed in writing to notify the tissue bank immediately of any suspected transmission of a communicable disease through transplanted tissue or a serious adverse event.

The tissue bank must in turn make a notification of SAE or untoward occurrence associated with the removal of human tissue primarily for research to MOH.

[1]*Human tissue transplantation" means the transplantation or grafting of any tissue from one part to the same/another part of a body of an individual or from the body of one individual to the body of another individual or individuals;*

Additional Requirements for TBs supporting Transplant Research

[Note: These requirements are for Transplantational Research TB: stores or supplies tissues for the purpose of use in research involving **human tissue transplantation.**]

Additional requirements before tissue is released, supplied or export

- PPIC authorisation of the release, supply or export of the tissue in writing;
- To provide the following information to the researcher receiving the tissue:
  - (i) source of tissue;
  - (ii) donor screening process and tests conducted to ensure product safety and compatibility; and
  - (iii) Any regulatory obligation of the tissue bank as a result of the removal, supply or export of the tissue

Tracking of health information relevant to safety and quality of tissue

The tissue bank must establish a system to ensure the health information relevant to safety and quality of each tissue is accurately tracked.

Management of tissue contamination

A tissue bank must establish a system to prevent or control the spread of any communicable disease which is or may be due to the contamination or infection of any tissue under its supervision and control. This system must at the minimum take into consideration the following:

- Traceability of tissue;
- Traceability of equipment and material used to process the tissue;
- Processing and preservation of tissue;
- Recall procedure for tissue.

Additional Requirements for TBs supporting Transplant Research

[Note: These requirements are for Transplantational Research TB: stores or supplies tissues for the purpose of use in research involving **human tissue transplantation.**]

Quality and safety management system

A tissue bank must establish a system to ensure the quality and safety of any tissue intended for use in human transplantation under its supervision and control. This system must at the minimum take into consideration the following:

- Qualification and training of personnel handling tissue;
- the method of processing and preservation to retain the biological function compatible with its intended use;
- Appropriate labelling and storage conditions;
- Management of quality control and inventory;
- Suitability and testing of tissue donors.

A tissue bank must establish an appropriate and effective system to ensure the **recall** of tissue which had been unintentionally or otherwise erroneously supplied for use in research involving human tissue transplantation.

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Thank You