OFFICE OF HUMAN RESEARCH PROTECTION PROGRAMME (OHRPP)

HUMAN BIOMEDICAL RESEARCH ACT (HBRA)

AND

ITS IMPLICATIONS ON STUDIES

Office of Human Research Protection Programme (OHRPP)

Group Research

Version_20 April 2023

National Healthcare Group

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Please note that these slides are intended as a guide to provide an overview of the

Human Biomedical Research Framework.

You are advised to read the following regulatory legislations in full to obtain a better understanding of its requirements:

- **Human Biomedical Research Act 2015**
- **Human Biomedical Research Regulations 2017**
- **Human Biomedical Research (Restricted Research) Regulations 2017**
- **Human Biomedical Research (Tissue Banking) Regulations 2019**
- **Human Biomedical Research (Tissue Banking and Notification – Exemption) Regulations 2019**
- **Human Biomedical Research (Requirements for Appropriate Consent – Exemption) Regulations 2019**

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1. HBRA implications on studies

a) Duties of Research Institution and Researchers

b) Is your study a HBR

c) Informed Consent Requirements

i. Taking appropriate consent

ii. Requirements of witness under HBRA

iii. Consent of Adults lacking capacity

iv. Consent of Minors and Minors lacking Capacity

v. Consent for Emergency Research

vi. Consent for research or removal or use of tissue for research in case of deceased persons

vii. Elements of Informed Consent according to HBRA

viii. Waiver of consent

d) Reporting of Expected SAE

e) NHG Monitoring Programme for HBR studies

2. Information, Resources & References

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RESEARCH INSTITUTION (RI)

Reference: NHG CRCS-CRP Forum 9 Dec 2016

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 under its supervision

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DUTIES OF RESEARCHERS

Section 22

Research Institution (RI)

2. Protocol approved

1.

3. ***Appropriate Consent obtained**

IRB

Must come under the supervision of an RI

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***

RESEARCH STARTS

Reference: NHG CRCS-CRP Forum 9 Dec 2016

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IS YOUR STUDY HBR?

Reference: HBRA 2015, Fourth Schedule Section 2, 31(1) and 62(1) and paragraph 1 of Third Schedule

Step 1: Is My Study Human Biomedical Research or Restricted Human Biomedical Research?		
Does this study involve: ☐ a. Human gametes or human embryos; **or** ☐ b. Cytoplasmic hybrid embryos; **or** ☐ c. The introduction of any human-animal combination embryo into an animal or human; **or** ☐ d. The introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into an animal at any stage of the development (including a prenatal animal foetus or animal embryo) ☐ e. Any entity created as a result of any process referred to in (c) **or** (d) above	**If YES** **If NO**	This is rHBR. Proceed to Step 2.

For more information about the HBRA, please refer to the MOH website via the link below:
https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act

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IS YOUR STUDY HBR?

Reference: HBRA 2015, Part 1, Section 3(1)

Step 2: Identify if your study objective falls within the scope of HBR

Does the intent of my study involve:		
❑ The prevention, prognostication, diagnosis or alleviation of any disease, disorder or injury affecting the human body; **or**	**If NO**	This is non-HBR
❑ The restoration, maintenance or promotion of the aesthetic appearance of human individuals through clinical procedures or techniques; **or**	**If YES**	Proceed to Step 3
❑ The performance or endurance of human individuals		

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IS YOUR STUDY HBR?

Reference: HBRA 2015, Part 1, Section 3(1)

Step 3: Identify if the methodology employed also falls under the scope of HBR

Does my study methodology involve:

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

This refers to any procedure administered **for research purposes (i.e. not part of standard care). If it has a physical, mental or physiological effect on participants, it is considered "interventional".*

- ❑ The use of any individually-identifiable biological material obtained from the human body; **or**
- ❑ The use of any individually-identifiable health information

If YES → This study falls under the scope of HBR.

If NO → This study is not HBR as it does not deploy the methodology as listed under this step.

Note: Your study falls under HBR only if you have answered "YES" for step 2 & 3.

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INFORMED CONSENT REQUIREMENTS

Reference: HBRA 2015 Part 3, Section 6 and HBR Regulations 2017, Part 4, sections 25

Appropriate consent must be obtained:

- ✓ **In writing;**
- ✓ **From the research subject personally unless otherwise;**
- ✓ **Full explanation provided and explained to the research subject or persons authorised to give consent on behalf and,**
- ✓ **In the presence of a prescribed witness.**

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REQUIREMENTS FOR A WITNESS FOR HBR STUDIES

Requirements for a WITNESS for HBR studies

Reference: HBRA, Part 3, Section 6(d) and HBR Regulations 2017, Part 4, sections 25

When is a witness required?

- If you are conducting a human biomedical research study that is regulated by the HBRA, appropriate consent must be taken in the presence of a witness.

Appropriate consent must be taken in the presence of a witness:

- Who is 21 years of age or older:
- Who has mental capacity; and
- Who must not be the same individual taking the appropriate consent.

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Reference: HBRA, Part 3, Section 6(d) and HBR Regulations 2017, Part 4, sections 25

Role of the witness

The witness must take reasonable steps to ascertain-

a) The identity of the individual giving the appropriate consent; **and**

b) That the consent was given voluntarily without any coercion or intimidation

Who can be the witness?

The witness may be a study team member unless the situation requires an impartial witness to be present (e.g. subjects who are unable to read)

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Exemption from need for a Witness to research subject's consent

Reference: Human Biomedical Research (Requirements for Appropriate Consent – Exemption) Regulations 2019

Exemption from need for a witness to research subject's consent

The presence of a prescribed witness is not required if the research is: -

a) not invasive;

b) not interventional; and

c) not restricted HBR *(refer to HBR 2015, Fourth Schedule for definition of restricted HBR)*

Note: For a HBR study where the subject is unable to read/ understand the language of the ICF, witness should also fulfill the impartial witness requirements. (NHG PCR SOP 501-C01 Informed Consent Document and Process, NHG Investigator's Manual 3rd edition Chapter 5.5 Subjects who are unable to read)

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Exemption from need for Witness to research subject's consent

Reference: Human Biomedical Research (Requirements for Appropriate Consent – Exemption) Regulations 2019

Exemption from need for witness to research subject's consent

The presence of a prescribed witness is not required if the following conditions are met:

i. the research is interventional but the intervention involves no more than minimal risk to the research subject;
ii. the research subject is able to read and sign the appropriate consent form; and
iii. the research is not restricted human biomedical research

Note: research is interventional if the research involves 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.)

Note: For a HBR study where the **subject** is **unable to read/ understand the language/ personally sign** the ICF, witness should also fulfill the ***impartial witness*** requirements.

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CONSENT IN ADULTS LACKING METAL CAPACITY

Mental Capacity Act (Chapter 177A) Section 4

A person who lacks capacity is one who lacks mental capacity in relation to a matter if, at the material time, he is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain.

An individual is unable to make a decision for himself if he is unable to:

a) Understand the information relevant to the decision;
b) Retain that information;
c) Use or weigh that information as part of the process of making the decision; or
d) Communicate his decision (whether by talking, using sign language or any other means).

CONSENT IN ADULTS LACKING MENTAL CAPACITY

Reference: HBRA 2015, Part 3, Section 7

Adults lacking mental capacity*

*According to Mental Capacity Act. (177A, Section A)

Is there a **Donee or Deputy?**

Donee: *The donee of that adult's lasting power of attorney;*

Deputy: *The deputy appointed by the court under the Mental Capacity Act*

In the order of priority stated

i. **the spouse;**
ii. **an adult son or daughter;**
iii. **either parent or a guardian;**
iv. **an adult brother or sister;**
v. **any other person named by the adult as someone to be consulted on the matter in question or on matters of that kind.**

Note: Research of comparable effectiveness cannot be carried out without the participation of this class of persons.

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CONSENT OF MINORS WHO HAVE SUFFICIENT INTELLIGENCE & UNDERSTANDING

Reference: HBRA 2015, Part 3, Section 8

Clinical research study involving minor

↓

Minor has sufficient intelligence and understanding

↓

Consent to be obtained from:
- ^Minor; and
- At least one adult parent or guardian of minor.

^Minor: below 21 years of age, never married.

IRB has waived parental consent requirement

↓

Consent to be obtained from minor

Note: Consent should be obtained from children who are 12 years old and above if they have sufficient intelligence and understanding to do so, together with consent from their legal representative.

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HBRA: WAIVER OF PARENTAL CONSENT

Reference: HBRA 2015, Part 3, Section 13(2)

The IRB may waive parental consent if:

i. Research involves **no more than minimal risk;**

ii. Waiver of parental consent will **not adversely affect** the rights and welfare of the research subjects; **AND**

iii. Research **may not be practicably carried out** unless there is such a waiver and the research proposal:

   a) 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;

   b) Is a **private and sensitive nature** that it is not reasonable to require permission **OR**

   c) Is within the description of such circumstances as may be prescribed.

Note: Consent must be obtained **from the minor** where the minor has **sufficient understanding and intelligence** to enable the minor to understand what is proposed in the biomedical research.

CONSENT OF MINORS WHO i) DO NOT HAVE SUFFICIENT INTELLIGENCE & UNDERSTANDING / ii) LACK MENTAL CAPACITY

i) Consent of Minors who do not have sufficient intelligence and understanding	ii) Consent of Minors who lack mental capacity
Reference: HBRA 2015, Part 3, Section 8	**Reference: HBRA 2015, Part 3, Section 8**
Clinical research study involving minor	Clinical research study involving minor
Minor who **does not** have sufficient intelligence and understanding	Minor who **lacks mental capacity**
Research cannot be carried out without the participation of the class of minors to which the minor belongs	Research cannot be carried out without the participation of the class of minors to which the minor belongs
Consent obtained from at least one adult parent **or** guardian of minor. Note: Assent should be obtained if the child is 6 years old and above together with consent from their legal representative.	Consent to be obtained from: i) Deputy (under Mental Capacity Act); **or** ii) At least one adult parent or guardian of minor.

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CONSENT FOR EMERGENCY RESEARCH

The IRB may consider waiver of appropriate consent for Emergency Research if:

a) Research subjects are in a **life-threatening** situation;

b) There is **no professionally accepted** standard of treatment or the available treatments are **unproven or are unsatisfactory**;

c) Collection of valid scientific evidence is **necessary** to determine the safety and effectiveness of a particular intervention or treatment;

d) There is a **prospect of direct benefit** to the research subjects

e) Obtaining appropriate consent is **not feasible** where
   (1) subjects will not have capacity within the time available to give their appropriate consent as a result of their medical condition or situation; **and**
   (2) no person who is authorise to give appropriate consent on behalf of the research subject

CONSENT FOR EMERGENCY RESEARCH

A Registered Medical Practitioner who is (1) a **specialist** in the specialty relating to the research and (2) who is **not involved** in the research as a researcher or supervisor to certify, *prior to the enrolment of the research subject* to the best of the specialist's knowledge of (a) to (e) [see previous slide].

f) The research **may not practicably be carried out unless there is a waiver**;

g) There is a provision made for one of the following, whichever occurs first:
   i. the **research subject** is **informed as soon as is practicable** after he or she regains capacity of his or her participation in the research and given an opportunity to withdraw from further participation; or

   ii. the **person who is authorised to give appropriate consent on behalf** of the research subject to be informed as soon as is practicable of the subject's participation and given an opportunity to request that the continued subject be withdrawn from further participation

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CONSENT FOR RESEARCH/ REMOVAL OR USE OF TISSUE FOR RESEARCH IN CASE OF DECEASED PERSONS

Reference: HBRA 2015, Part 3, Section 11

For use of the deceased person's **(1) Individually-identifiable biological material, body or any part of the body or health information** or *(2)* ***for the removal or use of human tissue for research,*** consent shall be obtained from:

i. the spouse;
ii. an adult son or daughter;
iii. either parent or a guardian of the deceased person at the time of the person's death
iv. an adult brother or sister;
v. the administrator or executor of the estate of the deceased person;
vi. any other person authorised or under obligation to dispose of the body of the deceased person.

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INFORMED CONSENT REQUIREMENTS

Elements of Informed Consent according to HBRA

Reference: HBRA 2015, Part3, Section 12(1), 12(2) and 14

Reference: HBRA Section 6(d) and HBR Regulations 2017, section 25

The NHG DSRB ICF Template has been updated to incorporate the consent elements as per HBRA and it can be found at https://www.research.nhg.com.sg > Resources > Ethics Forms and Templates

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WAIVER OF CONSENST FOR HBR STUDIES

Waiver of Consent for HBR studies

Reference: HBRA 2015, Fifth Schedule, Part 2, Section 3

Where the institutional review board is satisfied that —

a) the research cannot reasonably be carried out without the use of the human biological material or health information in an **individually-identifiable form**;
b) the process of obtaining consent from the person involves a **disproportionate amount** of effort and resources relative to the research requirements;
c) the use of the individually-identifiable human biological material or health information involves **no more than minimal risk** to the research subject or donor;
d) the waiver concerned **will not otherwise adversely affect the rights and welfare** of the research subject or donor; **and**
e) the human biomedical research or health information research would reasonably be considered to contribute to the **greater public good**.

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WAIVER OF CONSENT FOR HBR STUDIES

Waiver of Consent for HBR studies

Reference: HBRA 2015, Fifth Schedule, Part 2, Section 4

Individually-identifiable health information

Where the institutional review board is satisfied that —

a) the **individually-identifiable health information** was **obtained or compiled** before **1 November 2017**;
b) the research **cannot reasonably be carried out** without the use of the health information in an **individually-identifiable** form;
c) the use of the individually-identifiable health information involves **no more than minimal risk** to the research subject;
d) the waiver concerned **will not otherwise adversely affect the rights and welfare** of the research subject; **and**
e) the process of obtaining consent from the person will involve a **disproportionate amount of effort and resources** relative to the research requirements.

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WAVIER OF CONSENT FOR HBR STUDIES

Waiver of Consent for HBR studies

Reference: HBRA 2015, Fifth Schedule, Part 2, Section 5

Individually-identifiable human biological material

Where the institutional review board is satisfied that —

a) the **individually-identifiable human biological material** was **obtained or compiled** before **1 November 2017**;
b) the research cannot **reasonably be carried out** without the use of the human biological material in an **individually-identifiable** form;
c) the use of the individually-identifiable human biological material involves **no more than minimal risk** to the research subject;
d) the waiver concerned **will not otherwise adversely affect the rights and welfare** of the research subject; **and**
e) 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.

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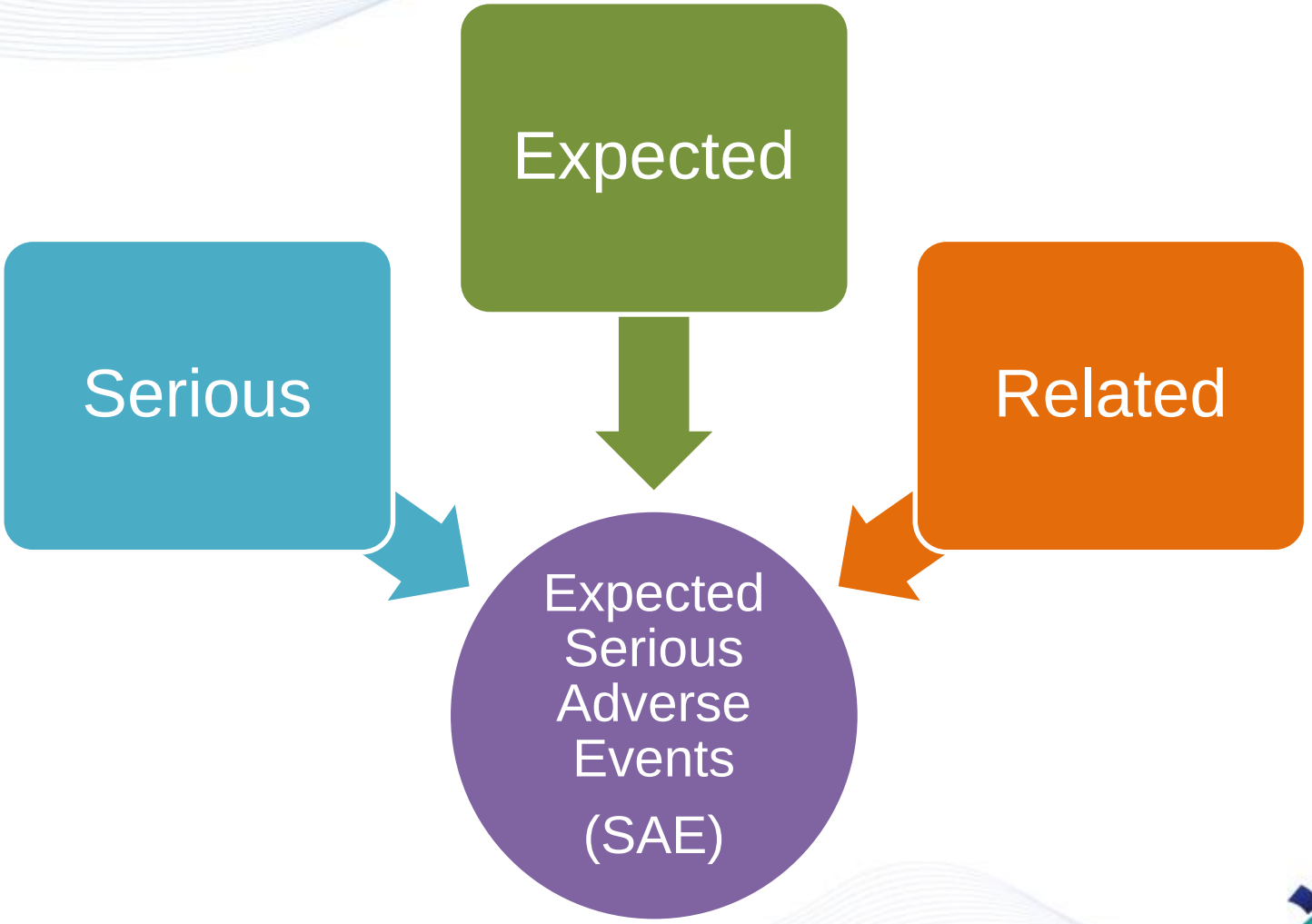
EXPECTED SERIOUS ADVERSE EVENTS (SAE)



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EXPECTED SERIOUS ADVERSE EVENTS (SAE)

Reference: HBRA 2015, Part 1, Section 2

Serious

Expected Serious Adverse Events (SAE)

Serious Adverse Events Definition

In relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

1) results in or contributes to death;
2) is life threatening;
3) requires inpatient hospitalisation or prolongation of existing hospitalisation;
4) results in or contributes to persistent or significant disability/ incapacity;
5) results in or contributes to a congenital anomaly or birth defect; or
6) results in such other event as may be prescribed.

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EXPECTED SERIOUS ADVERSE EVENTS (SAE)

These are risks or events reported in the Investigator's Brochure and listed in the consent form or other study documents.

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EXPECTED SERIOUS ADVERSE EVENTS (SAE) - HBRA

Related (including *possibly related) to participation in the research.

The following conditions might help to access causality. The event:

a) has a reasonable temporal relationship to the intervention,

b) could not have been produced by the underlying disease states,

c) could not have been due to other non-study interventions,

d) Follows a known pattern of response to the intervention, or

e) Disappears with cessation of intervention

**possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.*

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EXPECTED SERIOUS ADVERSE EVENTS (SAE)

Reporting Timeline effective 1 Nov 2017

1) Only research studies that are regulated by the Human Biomedical Research Act (HBRA) will need to submit Expected SAE to DSRB.

2) Reportable events occurred in both Singapore and overseas sites should be reported within the stipulated timeline (as per point 3.)

3) PI should report Expected SAEs as soon as possible but no later than 7 calendar days after first knowledge by the PI and any additional relevant information should be reported within 8 calendar days of making the initial report.

Note: For studies approved by other IRB(s) via mutual recognition arrangement (e.g. NHG study approved by CIRB), expected SAE(s) reporting should follow the requirements set by the approving IRB.

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EXPECTED SERIOUS ADVERSE EVENTS (SAE)

For DSRB approved studies

Reference: PCR SOP 501-C01 UPIRTSO and Expected SAE

Is the DSRB approved study a HBR study?

YES

Submit the following:

1. **Unanticipated problems involving risks to subjects of others (UPIRTSO)**
2. **Expected SAE**

(submission via ROAM 9 April 2018)

NO

Submit the following:

1. **UPIRTSO**

*These problems have to be **(1) unexpected and (2) related** or possibly related to study, except Local death (regardless of causality and expectedness)*

Reference: Guide to Reporting Expected SAE for site (via ROAM)
https://www.research.nhg.sg > Resources > ROAM Guidebooks > ROAM Guides

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PROACTIVE MONITORING FOR HBR STUDIES

Reference: HBRA Part 5, Section 23

Every research institution must, in respect of any human biomedical research which is carried out under its supervision and control — (a) supervise, review and **proactively monitor the conduct** of the research.

For more information on NHG Monitoring Programme, please refer to the following link: https://www.research.nhg.sg > Ethics & Quality > Research Quality > Monitoring

NHG MONITORING PROGRAMME FOR DSRB APPROVED HBR STUDIES

Under this Programme, **all NHG PI-Initiated Human Biomedical Research (HBR) studies** conducted in **NHG institutions** will be subjected to monitoring.

Objectives of NHG Monitoring Programme:

- Safeguard the safety and well-being of the research participants;
- Ensure good quality and integrity of the research data;
- Ensure the conduct of the study is in accordance to applicable regulations, policies and guidelines; and to
- Fulfil the responsibility as a RI according to HBRA.

Reference: https://www.research.nhg.sg > Ethics & Quality > Research Quality > Monitoring

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How are the studies monitored?

Risk Cat.	Criteria		Mode of Monitoring
1	All **Exempt** Studies		PI Self-Assessment Form (PISAF)
2A	All **Expedited** studies with Industry-Sponsored Monitoring available		
	All PIs		As per Sponsor's requirements.
2B	All **Expedited** studies with **NO** Industry-Sponsored Monitoring		
	Waiver of consent conducted by New PI^ *(New PI, no prior research experience as PI before)*		PISAF (Part of existing programme)
	No waiver of consent conducted by New PI^ *(New PI, no prior research experience as PI before)*		**PISAF (Mandatory)**
	All other PIs		PISAF
3	**Full Board** studies with Industry-Sponsored Monitoring available		As per Sponsor's requirements.
	Full Board studies with **NO** Industry-Sponsored Monitoring		
	Tier A	Which involves: • Vulnerable Population *(as per DSRB def: Studies involving children, pregnant women, foetuses and neonates, cognitively-impaired persons and prisoners)* • Restricted Research *(as defined in Fourth Schedule of HBRA)* • Devices *(Includes all Unregistered products, and Registered Classes B, C, D in accordance to HSA Medical Device Guidance GN13 (May 2014) Risk Classification)* • Surgical Procedures • PI who has never conducted a Full Board study approved by DSRB previously	Remote + Onsite Monitoring
	Tier B	All other Full Board studies that do not fall into Category 3 Tier A	Mandatory PISAF + Onsite Monitoring

INFORMATION, RESOURCES & REFERENCES

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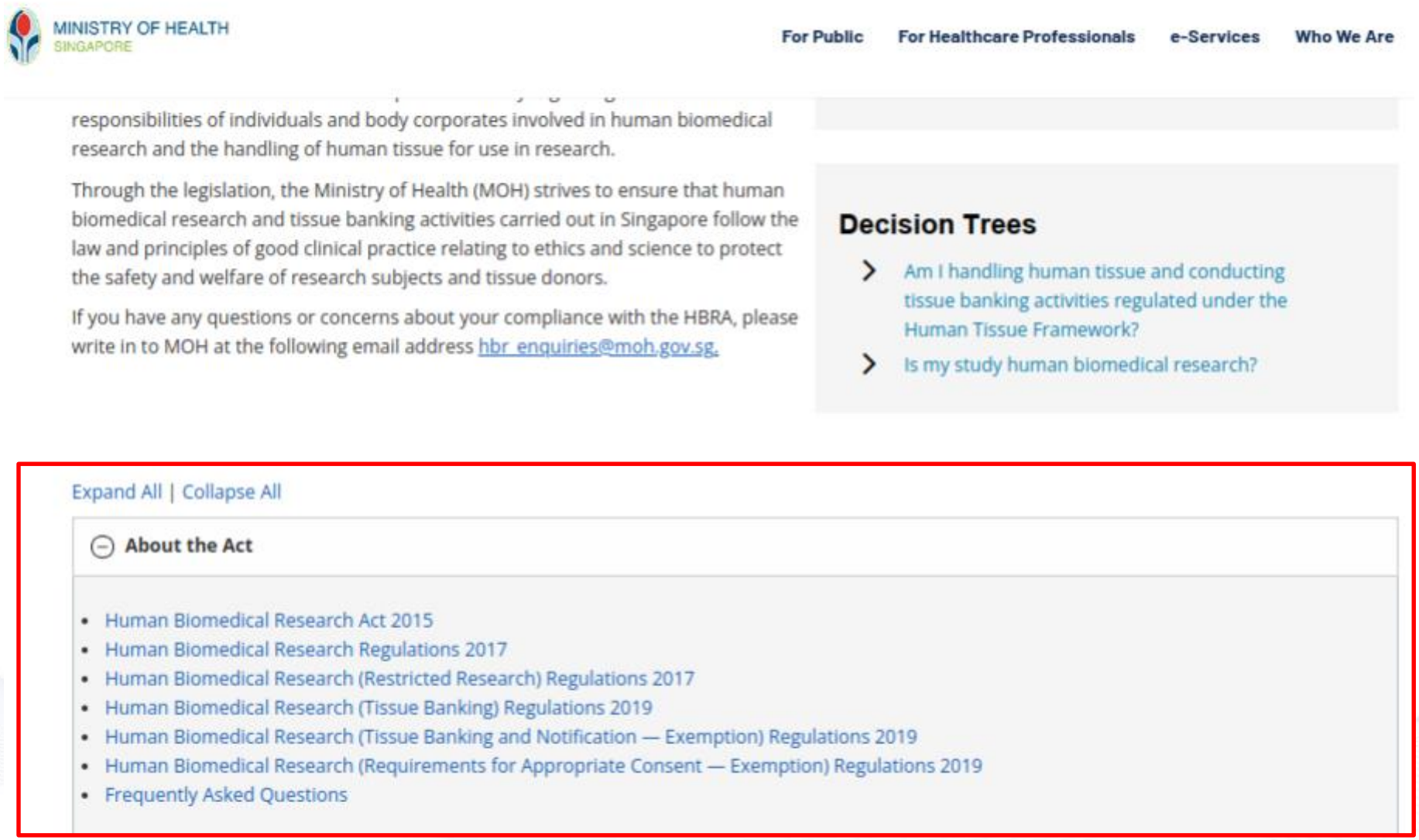
INFORMATION, RESOURCES & REFERENCES

For more information on the Human Biomedical Research Act and its subsidiary legislation, refer to the following link: https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act



RESOURCES

For reporting of Expected Serious Adverse Events (SAE) guide and template, please refer to the following website-

1. Guide to Reporting Expected SAE for site https://www.research.nhg.com.sg > Resources > ROAM Guidebook > ROAM Guide

2. Expected Serious Adverse Events (SAE) Reporting Form & Guide https://www.research.nhg.com.sg > Resources > Ethics Forms & Templates

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QUERIES TO HBRA?

Queries regarding HBRA?

Please write to the NHG Research Institution (RI) at NHGRISecretariat@nhg.com.sg

To access the list of RI that notified MOH of their operations, go to https://www.gov.sg > Ministry of Health > About the Human Biomedical Research Framework > Research Institution that Notified MOH of their Operations

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THANK YOU FOR YOUR KIND ATTENTION

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