

# **INVESTIGATOR'S MANUAL**

**4th EDITION**

***Research Ethics &  
Regulatory Requirements  
For Research Submitted to***

**NHG DSRB**



Adding years of healthy life

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### National Healthcare Group Member Institutions

- Tan Tock Seng Hospital
- Institute of Mental Health
- National Healthcare Group Polyclinics
- National Skin Centre
- NHG College
- NHG Diagnostics
- NHG Pharmacy
- Primary Care Academy
- Khoo Teck Puat Hospital
- Yishun Community Hospital
- Geriatrics Education and Research Institute
- Admiralty Medical Centre
- Woodlands Integrated Health Campus

### Partner Institutions

Institutions and organisations with ethics governance under the NHG DSRB

- National University Health System
- Agency for Integrated Care
- Ang Mo Kio Thye Hua Kwan Hospital
- Dover Park Hospice
- Health Sciences Authority
- Health Promotion Board
- Lilly Centre for Clinical Pharmacology
- Singapore Institute for Clinical Sciences, A\*STAR
- Singapore Institute of Food and Biotechnology Innovation (SIFBI), A\*Star
- Skin Research Institute of Singapore (SRIS), A\*Star

### IRBs with Mutual Recognition Agreement with DSRB

- SingHealth CIRB

### IRBs with Cooperative Agreements with DSRB

- NTU IRB
- NUS IRB

# FOREWORD

Clinical research in Singapore has been experiencing an unprecedented pace of growth, both qualitatively and quantitatively. Our healthcare institutions and research communities have been investing a considerable amount of resources into the search for new knowledge and new solutions in treatment and in healthcare delivery. Current trends within NHG's activities in research and innovation reflect a congruent course.

In 2007, the NHG Domain Specific Review Board (DSRB) received only 104 study applications submissions for ethics review. In 2018, this figure stands at 1221 study submissions. The statistics for the number of active NHG Principal Investigators (PIs) are equally encouraging – in 2009, 338 PIs submitted proposals for their research studies. This number has grown to 772 in 2018. Such exponential increases are reflective of NHG's robust research infrastructure to support continued growth in this sector.



Amidst research growth and evolution through the years, the fundamentals of research ethics have endured and remained relevant. The professional obligation to protect human volunteers and to ensure the scientific integrity and ethical justification of every research study remain the pillars that nurture public trust in the biomedical research endeavour. Ethical codes and guidelines such as the Nuremberg Code (1946), the Declaration of Helsinki (1964), the Belmont Report (1979) and the International Council For Harmonisation (ICH) E6 (R2) Good Clinical (GCP) Guidelines 2016 are incorporated and referenced by the NHG DSRB in its attempt to uphold a high standard of research ethics in NHG and in Singapore.

To ensure that our growing pool of PIs understand these research ethics meaningfully, the NHG Office of Human Research Protection Program (OHRPP) published the first edition of the Investigator's Manual in August 2009, as a handy reference tool catering to both new and experienced investigators alike. This publication amalgamates the regulatory requirements, ethical provisions and institutional policies governing research conduct, allowing PIs to adeptly navigate the formidable convolutions of the research maze. Since the launch of the Investigator's Manual, clinical investigators and other members of the research community have given unequivocal affirmation on the utility and value of this publication in providing an essential compass for their research activities.

In tandem with the strong interest in research in Singapore, the local regulations and regulatory requirements have also evolved tremendously. The Medicines Act was first enacted in 1976, but has since seen some of its regulatory controls for clinical trials ported over to the Health Products Act. Human biomedical research, an area previously largely overseen by the local institutional review boards in the absence of applicable laws, now has the newly minted Human Biomedical Research Act to look to for regulatory governance. While these new regulations do convert many key ethical guidelines into mandatory standards of conduct and procedures to be met by research institutions and researchers, it is both desirable and conceivable that they will, in the long run, catalyse the development of an ethical research culture and ultimately, a mature environment facilitating exponential advancement in biomedical research.

With the publication of the updated Fourth Edition of the Investigator's Manual, I hope that principal investigators and clinical researchers alike will find this manual both practical and useful, and actively use it to improve the ethical standards of their research.

Yours faithfully

**Associate Professor Chin Jing Jih**

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# ABBREVIATIONS

Below is a list of common abbreviations that will be used throughout this Investigator's Manual.

ABPI	Association of the British Pharmaceutical Industry
BAC	Bioethics Advisory Committee
CAPA	Corrective Action and Preventive Action
CFR	US Code of Federal Regulations
CIOMS	Council for International Organisations of Medical Sciences
CIRB	SingHealth Centralised Institutional Review Board
CITI	Collaborative Institutional Training Initiative
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRM	Clinical Research Materials
CRU	Clinical Research Unit
CTA	Clinical Trial Authorisation
CTC	Clinical Trial Certificate
CTN	Clinical Trial Notification
DCF	Data Collection Form
DHHS	US Department of Health and Human Services
DNA	Deoxyribonucleic acid
DR	Department Representative
DSMB	Data Safety Monitoring Board
DSRB	Domain Specific Review Board
FCOI	Financial Conflict Of Interest
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HRPP	Human Research Protection Programme
HBR	Human Biomedical Research
HBRA	Human Biomedical Research Act
HIV	Human Immunodeficiency Virus
HSA	Health Sciences Authority

ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICOI	Institutional Conflict Of Interest
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IO	Institution Officer
IR	Institution Representative
IRB	Institutional Review Board
MD	Medical Device
MOH	Ministry of Health Singapore
MP	Medicinal Product
NHG	National Healthcare Group
NMEC	National Medical Ethics Committee
NUS	National University of Singapore
OHRPP	NHG Office of Human Research Protection Programme
PCR	Proper Conduct of Research
PDPA	Personal Data Protection Act
PDPC	Personal Data Protection Commission
PI	Principal Investigator
QA	Quality Assessment
QI	Quality Improvement
REC	NHG Research Ethics Committee
RI	Research Institution
ROAM	NHG Research Online Administration & Management System
SAE	Serious Adverse Event
SBE	Social, behavioural and educational (modules from CITI)
SDC	Singapore Dental Council
SMC	Singapore Medical Council
SOP	Standard Operating Procedures
STD	Sexually Transmitted Diseases
TP	Therapeutic Product

UPIRTSO	Unanticipated Problems Involving Risks To Subjects or Others
USADR	Unexpected Serious Adverse Drug Reactions

# **CHAPTER 1**

# **RESEARCH GOVERNANCE**

- 1.1    Office of Human Research Protection Programme (OHRPP)**
- 1.2    Role and Structure of the Domain Specific Review Board (DSRB)**
- 1.3    Role of Institutions, Department and Institution Representatives, Investigators and Other Study Team Members**
- 1.4    Research Regulations and Guidelines**
- 1.5    Does My Study Require DSRB Approval?**
- 1.6    References and Suggested Readings**

## **1.1 Office of Human Research Protection Programme (OHRPP)**

The formation of the OHRPP signifies NHG's commitment to protecting research through a comprehensive setup of programmes, framework and functions. With in-house support and expertise, the OHRPP is better positioned to drive improvement and innovation that can directly benefit the research community. While continuing to forge close partnerships with institutions and agencies within and outside NHG, the OHRPP promotes community outreach and education for the public. The OHRPP will also take the lead in advocating best practices in human research protection through merging knowledge and experience learnt from our counterparts in the west and implementing them in Asia's context.

The goals of the OHRPP are to ensure the safety and well-being of human research subjects, and to advocate their rights through:

- a. Efficient and high quality ethics review
- b. Education on human research protection
- c. Quality assurance and continuous improvement
- d. Engagement of public and research partners

### **In its entirety, the OHRPP comprises 5 divisions:**

<b>DSRB Operations &amp; Management</b>	All research involving NHG patients, NHG staff, NHG premises, or NHG facilities are to be reviewed and approved by the NHG DSRB prior to initiation. The DSRB's primary role is to safeguard the rights, safety, and well-being of human research participants in NHG and her institutions, as well as ensure high quality and efficient review of research applications.
<b>Research Quality Management (RQM)</b>	RQM provides quality assurance activities to ensure that research protocols approved by the DSRB are carried out ethically and in accordance with all applicable regulations.
<b>Research Education (RE)</b>	RE develops training programmes and resources, as well as conducts educational support initiatives for investigators and researchers.
<b>Partnerships &amp; Outreach (P&amp;O)</b>	P&O oversees the extension of ethics review services and oversight to external healthcare set-up and agencies, providing a common platform of ethics review and establishing common standards of research conduct in different institutions.
<b>Research Compliance Unit (RCU)</b>	The RCU provides administrative support to the NHG Principal Person In Charge (PIC), Research Committee (RC), Tissue Compliance Committee (TCC), Research Data Oversight Committee (RDOC) and also oversees the propagation of a Responsible Conduct of Research (RCR) culture and promotes RCR awareness within the research community. RCU also supports other committees on RI related matters and supports functions of the NHG RI to ensure research in NHG is in compliance with the HBRA.

## **1.2 Role and Structure of the Domain Specific Review Boards (DSRB)**

The DSRB is an independent committee constituted by medical, scientific members and laypersons, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a research study by reviewing, approving and providing continuing review of research studies and amendments, and of the methods and materials to be used in obtaining and documenting informed consent of the research subjects.

The NHG Group Chief Executive Officer appoints members to the DSRB, for NHG RI. Each domain will consist of at least 5 members, who collectively have the qualifications and experience to carry out the DSRB's stated objectives and terms of reference to review and evaluate the ethical and scientific aspects of the proposed research studies.

Other officials of institutions which conduct research under the oversight of NHG DSRB, may not override the decision of DSRB (or REC, where applicable). The REC is a committee comprising the DSRB chairpersons and laypersons, which collectively establishes and oversees the policies and implementation of the HRPP in NHG.

There are currently 5 biomedical domains (A –E) on broad but related disease groupings, and a Population Health Domain (F). Each board is made up of 11-15 members and is constituted in compliance with the HBRA and GCP guidelines.

The purpose of such an arrangement is to ensure that more appropriate expertise can be concentrated within each domain to assess the scientific and ethical merits of each study submitted for ethics review.

The specialties under each domain of DSRB are shown in figure 1 below.

Figure 1: Specialties under each DSRB domain

Domain A	Domain B	Domain C
<ul style="list-style-type: none"><li>• Ophthalmology</li><li>• Psychiatry</li><li>• Neurology/ Neurosurgery</li><li>• Genetics</li><li>• Geriatric Medicine</li><li>• Palliative Medicine</li></ul>	<ul style="list-style-type: none"><li>• Oncology</li><li>• Hematology</li><li>• Pathology</li><li>• Paediatrics</li><li>• Respiratory Medicine</li></ul>	<ul style="list-style-type: none"><li>• Cardiovascular Science</li><li>• Pharmacology</li><li>• Emergency Medicine</li><li>• Endocrinology</li><li>• Diagnostic Imaging</li><li>• Family Medicine*</li></ul>
Domain D	Domain E	Domain F – Population Health
<ul style="list-style-type: none"><li>• Obs/Gynaecology</li><li>• Anaesthesia</li><li>• Surgery#</li><li>• ENT</li><li>• Dentistry</li><li>• Sports and Rehab Medicine</li><li>• Allied Health</li></ul>	<ul style="list-style-type: none"><li>• Infectious Disease</li><li>• Gastroenterology</li><li>• Renal Medicine</li><li>• Rheumatology/Immunology</li><li>• Dermatology</li></ul>	<ul style="list-style-type: none"><li>• Health Services and Outcomes Research</li><li>• Education Research</li><li>• Research on Prevention and Health Promotion Programs</li><li>• Social and Behavioral Research</li><li>• Epidemiological Research</li><li>• Community-based Participatory Research</li></ul>

\*Non organ/disease specific Family Medicine studies only.  
# Includes General Surgery, Orthopaedic Surgery, Plastic Surgery and Urology.

With effect from 2 Nov 2012

Genetics studies should be submitted to the DSRB domains according to the relevant disease groupings or medical specialty that is intended to be studied. Non disease specific genetics studies shall continue to be submitted to DSRB A for review.

## **1.3 Role of Institutions, Department and Institution Representatives, Investigators and Other Study Team Members**

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### **1.3.1 Institutions**

The DSRB, as well as the institutions, must approve a research proposal before it can be conducted in institutions under the oversight of NHG DSRB. The protection of human subjects in research is a collaborative effort by the Research Institution (RI), DSRB and all institutions under the oversight of NHG DSRB. While the DSRB is an independent review committee responsible for ensuring that the research proposal protects the well-being, safety and rights of the research subjects, each institution ensures that the proposal is in keeping with the relevant regulatory requirements, its overall research direction, objectives, standards and image.

### **1.3.2 Department Representative (DR)**

The DR plays a key role in ensuring that a research study is in keeping with the research objectives, image and standards of the relevant departments and institutions. The role of a DR is to provide an overview assessment of the significance, concept, and innovation of a research study. The DR should also determine whether the PI is adequately trained, qualified, possesses sufficient time and resources to carry out the research study. The DR will endorse all applications made to the DSRB. In general, the DR will be the Head of Department, Chief, Department Research Head or equivalent of the PI's and site PI's department. In some departments, alternative persons may be appointed as DRs, provided he / she is able to adequately perform the responsibilities of a DR. Where appropriate, the Head / Chief of a Division (e.g. Division of Medicine) who oversees several departments may comment in lieu of one of his / her Head / Chief of department. Should the Head or Chief be the PI or be part of the study team, then their reporting officer should be the DR.

*For more information, please refer to <https://www.research.nhg.com.sg> > Resources > ROAM Guidebooks > Department Representative Guidebook.*

### **1.3.3 Institution Representative (IR)**

The IR has been determined by each institution as the authority to approve any research study to be conducted in the institution. The role of the IR is to assess if the research is in keeping with the institution's research objectives, image and standards. In general, the IR's role is not to evaluate the scientific or ethical merits of the research study (although they may offer their comments), as all these will be considered by the DR, DSRB or a grant approving body (if applicable).

The IR must endorse the application before it may be reviewed by the DSRB. This authority is generally delegated to one of the following persons:

- a. Director of Research (or equivalent); or
- b. Chairperson of a specially appointed committee for this purpose; or

- c. Chairman Medical Board.

For multi-centre studies, the IR of each of the site PIs must endorse the application to be conducted at his / her institution. The DSRB will proceed to review the application as long as the IR of the overall PI has endorsed the application. A study may not be initiated at a study site if the site PI did not obtain his / her IR's endorsement.

*For more information, please refer to <https://www.research.nhg.com.sg> > Resources > ROAM Guidebooks > Institution Representative Guidebook.*

#### **1.3.4 Investigators and Other Study Team Members**

The PI is the overall person responsible for the proper conduct of research. In general, there is only one person who is appointed as the PI for each research study. The PI is allowed to delegate study-related tasks to qualified/ trained members of the research study team (e.g. co-investigators or collaborators). When the tasks have been delegated, the PI must ensure that the delegation log is updated with each team member's assigned responsibilities prior to the start of the research. The PI and all study team members have the responsibility to comply with DSRB policies and applicable regulatory requirements.

For multi-centre studies within NHG and all institutions under the oversight of NHG DSRB, each institution should have a site PI who is responsible for the conduct of the study in his / her institution. One of the site PIs should be designated as the overall PI for the study, who is responsible for the coordination of investigators at different institutions participating in the multi-centre study, including but not limited to communication with the DSRB.

*For more information on the requirements for PIs, please refer to chapter 3 The Study Team.*

### **1.4 Research Regulations and Guidelines**

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All research involving patients, staff, premises, or facilities of all institutions under the oversight of NHG DSRB must be reviewed and approved by NHG DSRB prior to initiation.

All research reviewed and approved by the DSRB for conduct in institutions under the oversight of the DSRB must comply with DSRB's requirements as outlined in this manual. These requirements are compiled based on local and international regulations, some of which are listed below:

- a. Health Products Act and its subsidiary legislation – applicable for clinical trials of therapeutic products and Cell, Tissue and Gene Therapy Products which include chemical drugs, biologics, Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs);
- b. Medicines Act and its subsidiary legislation – applicable for clinical trials of medicinal products include complementary health products (e.g. Chinese proprietary medicines);
- c. Human Biomedical Research Act (2015) and its subsidiary legislations – applicable for human biomedical research studies and donation of human tissues;

- d. Personal Data Protection Act and its subsidiary legislation – to regulate the collection, use and disclosure of personal data;
- e. ICH GCP E6(R2) – all clinical trials are required to abide by GCP guidelines;
- f. US DHHS Regulations 45 CFR 46 – applicable for research funded by US federal funds e.g. National Institutes of Health (NIH), National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAIDS), etc.;
- g. US FDA Regulations 21 CFR 50 / 56 / 812 – when the research is being conducted under an Investigational New Drug (IND) Application or Investigational Device Exemption (IDE), or when the results of research are intended to be submitted to FDA;
- h. Bioethics Advisory Committee report on Ethics Guidelines for Human Biomedical Research (published October 2021);

All organisational officials, researchers and research staff (including students involved in conducting research), DSRB chairpersons and members and employees of NHG's HRPP, are required to abide by the abovementioned regulations and guidelines.

#### **1.4.1 Definition of Research and Other Important Definitions**

##### **I. The Health Products Act**

**CLINICAL TRIAL** - An investigation in respect of a health product that involves human subjects and that is intended to:

- a. Discover or verify its clinical, pharmacological or pharmacodynamics effects;
- b. Identify any adverse effect that may arise from its use;
- c. Study its absorption, distribution, metabolism and excretion; or
- d. Ascertain its safety or efficacy;

“Efficacy”, in relation to a health product that is a device, includes the ability of the device to properly carry out its intended purposes.

##### **II. Medicines Act**

**CLINICAL TRIAL** - An investigation or series of investigations consisting of the administration of one or more medicinal products of a particular description by, or under the direction of:

- (a) A doctor or dentist to one or more of his patients; or

Two or more doctors or dentists, each product being administered by or under the direction of one or other of those doctors or dentists to one or more patients, where (in any such case) there is evidence that medicinal products of that description have effects which may be beneficial to the patient or patients in question and the administration of the product or

products is for the purpose of ascertaining whether, or to what extent the product has, or the products have, those of any other effects, whether beneficial or harmful.

### **III. ICH GCP**

**CLINICAL TRIAL** – Any investigation in human subjects intended to discover or verify the clinical, pharmacological and / or other pharmacodynamics effects of an investigational product(s), and / or to identify any adverse reactions to an investigational product(s), and / or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and / or efficacy.

**SUBJECT / TRIAL SUBJECT** – An individual who participates in a clinical trial, either as a recipient of the investigational product(s), or as a control.

### **IV. Human Biomedical Research Act**

#### **HUMAN BIOMEDICAL RESEARCH -**

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,

And 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.

Research that involves:

- a. Human embryos or human gametes; or
- b. Cytoplasmic hybrid embryos; or
- c. The introduction of any human-animal combination embryo into an animal or a 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 development (including a pre-natal animal foetus or animal embryo); or
- e. Any entity created as a result of any process referred to in paragraph (c) or (d).

**RESEARCH INSTITUTION** - A body of persons, whether corporate or unincorporate or other organisation, or ministry or department of the Government who or which —

- a. Engages, directly or indirectly (either through contractual or other arrangements), one or more researchers to conduct human biomedical research in Singapore; and
- b. Exercises supervision and control over human biomedical research conducted in Singapore by the researchers the institution has engaged

## V. US DHHS Regulations

**RESEARCH** is a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

**HUMAN SUBJECT** or participant is a living individual about whom an investigator conducting research:

- a. Obtains data information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens
- b. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

**INTERVENTION** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

**INTERACTION** includes communication or interpersonal contact between investigator and subject.

**PRIVATE INFORMATION** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

## VI. US FDA Regulations

**CLINICAL INVESTIGATION** is any experiment that involves a test article and one or more human participants and that is one of the following:

- a. Subject to requirements for prior submission to FDA; or
- b. Not subject to requirements for prior submission to FDA, but the results of which are intended to be submitted later to, or held for inspection by FDA as part of an application for a research or marketing permit.

**HUMAN SUBJECT** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. For studies involving investigational devices (i.e. requiring an IDE), human subject is defined as a human who participates in an investigation either as individual or on whom or on whose specimen an investigational device is used or as a control. A subject may be either a healthy individual or a patient.

**TEST ARTICLE** means any drug for human use, biological product for human use, medical device for human use, human food additive, colour additive, electronic product, or any other article subject to FDA regulation.

## **VII. BAC Report on Ethics Guidelines for Human Biomedical Research (Published October 2021)**

**HUMAN BIOMEDICAL RESEARCH** refers to any research done for the ultimate purpose of studying, diagnosing, treating or preventing, any disease, injury, disorder, or condition of the human mind or body, and which entails the involvement of humans, human biological materials or information derived from humans or human biological materials. Also included is research on human physiological processes.

**PERSONAL INFORMATION** is any identifiable information about an individual, living or dead. It not only includes personal particulars, but also details of medical conditions, as well as information disclosed or derived in the process of healthcare management. In the research context, it will include any information collected, used or generated as part of the research process.

**HUMAN GENETIC RESEARCH** is the study of genes, their functions, how they are associated with health and disease, and how genetic and environmental factors influence health. This research may involve subjects directly and specifically, or it may involve stored tissue samples or personal information from medical records or other databases. It may involve the study of a specific gene, multiple genes, gene-environment interactions, or the entire genome in seeking to establish associations between genomic variants and diseases or specific traits.

### **1.4.2 Principles of Ethical Research**

Ethical research is research that:

- a. Upholds the core ethical principles of respect for persons, beneficence and justice.
- b. Protects rights, safety and well-being of human subjects.
- c. Complies with all applicable regulations and guidelines.

DSRB's research policies are based on local and international ethical guidelines, some of which are listed below:

- a. Belmont Report;
- b. Declaration of Helsinki;
- c. Human Biomedical Research Act 2015
- d. The Nuremberg Code

### **I. The Belmont Report**

The Belmont Report describes three core ethical principles for human research:

- a. Respect for persons – recognition of the personal dignity and autonomy of individuals and special protection of these persons with diminished autonomy, e.g. the need to obtain informed consent.
- b. Beneficence – entails an obligation to protect persons from harm by maximizing anticipated benefits and minimising possible risks of harm, e.g. the need to engage in a risk / benefit analysis and to minimise risks. Justice – requires that the benefits and burdens of research be distributed fairly, e.g. the need to have a reasonable inclusion and exclusion criteria.

## **1.5 Does My Study Require DSRB Approval?**

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### **1.5.1 Examples of Research Activities that Require DSRB Approval**

Activities that involve systematic investigation and are designed to develop or contribute to generalisable knowledge are considered research and will require review and approval by NHG DSRB. This includes clinical trials, epidemiological research; retrospective medical records review research, and genetic research.

**CASE SERIES** – A series of 3 or more subjects qualifies as a research project and hence should be submitted for review and approval by the DSRB prior to initiation.

**DATABASE STUDIES** – Databases that are created with the intention of using the stored data for future research should be registered as a Standing Database (SDB). Databases which are created as part of a previous IRB approved research study that has since been completed, may be set up to store data for possible research. Such databases should be registered as a SDB upon completion of the research study.

You may refer to the NHG Research Website at <https://www.research.nhg.com.sg> > Conducting Research > Standing Databases (SDB) for more information on how register such databases.

Individual research projects extracting data from SDBs will require DSRB review and approval.

*For more information on standing databases, please refer to chapter 8 Standing Database.*

**HUMAN TISSUE BANK / REPOSITORIES** – Operation of human tissue repositories and related data are subjected to oversight of the respective Research Institution (as defined in the HBRA).

Tissue Bank (TB) review boards will review and approve protocols specifying the conditions under which tissues and related data may be accepted and shared and ensuring adequate provisions to protect the privacy of donors and maintain the confidentiality of data. DSRB supports the review of TB related submissions to ensure that the recruitment and consent process of donors complies with ethics requirements and HBRA.

You may refer <https://www.research.nhg.com.sg> > Conducting Research > Human Tissue Framework for more information.

**QUALITY ASSESSMENT / QUALITY IMPROVEMENT (QA / QI)** – The following checklist in table 1 may be used to determine if a QA / QI study requires DSRB review. Where the response to all questions in the QA / QI checklist is “No”, and where there is no intention to share the information with others (i.e. contributing to generalizable knowledge) at the onset of the study, the QA / QI study will not be subject to DSRB review.

Table 1: Checklist to determine if a QA / QI study requires DSRB review

Where the response to all these questions is “No”, the QA/QI study is unlikely to require an IRB review. If you require a formal IRB letter of waiver from review, fill in and submit the DSRB exempt application form for review.			
S/N	Questions	Yes	No
1.	Does the proposed quality assurance activity require additional consent from subjects, beyond what is already obtained for clinical practice?		
2.	Does the proposed quality assurance activity pose any risks for subjects beyond those of their routine care?		
3.	Does the proposed quality assurance activity impose a burden on subjects beyond that experienced in their routine care?		
4.	Is the proposed quality assurance activity to be conducted by a person who does not normally have access to the subjects' records for clinical care?		
5.	Does the proposed quality assurance activity risk breaching the confidentiality of any individuals' personal information, beyond that experienced in the provision of routine care?		
6.	Does the proposed quality assurance activity involve any clinically significant departure from the routine clinical care provided to the subjects?		

7.	Does the proposed quality assurance activity involve randomization?		
8.	Does the proposed quality assurance activity involve the use of a control group or a placebo?		
9.	Does the proposed quality assurance activity seek to gather information about the participant beyond that collected in routine clinical care?		
10.	Does the proposed quality assurance activity potentially infringe the rights, privacy or professional reputation of health care providers or the institution(s)?		

### **1.5.2 Examples of Research-Like Activities that May Not Require DSRB Approval**

Case Reports – Do not involve systematic investigation; however the intent is to contribute to generalisable knowledge. Case reports on one or two subjects are not considered as human subject research. (Studies involving three or more subjects are considered case series and will require DSRB approval. Please refer to the description of case series in the above section.)

Outbreak Investigations – Outbreak investigations are important activities that benefit public health. Subjecting these to research standards might compromise these activities. As such, outbreak investigations are not considered to be research and do not require DSRB review. However, any interventional studies conducted during an outbreak would require review and approval by the DSRB and / or other clinical Committees. The DSRB will make an effort to expedite the review and approval process for such protocols.

Disease Management – Disease management projects that do not require the subjects to undergo additional burdens or risks do not require review and approval by the DSRB.

Infection Control – Investigations carried out as part of an infection control program are not considered as research and these do not require review by the DSRB.

Quality Assessment (QA) / Quality Improvement (QI) – Please refer to the description of QA / QI studies in section 1.5.1 above. Where the response to all questions in the QA / QI checklist is “No”, the QA / QI study will not be subject to DSRB review.

Studies Involving Anonymised Data and/or Human Biological Materials – These studies do not meet the definition of human subjects research, as there is no use of identifiable private information or identifiable biospecimens. These studies do not require review and approval by the DSRB.

### **1.5.3 Determination of Research Status**

There are many research-like activities that are conducted as part of quality assessment and improvement, infection control, disease management etc., that may not meet the definition of research and hence do not need DSRB review and approval. Further, new innovative therapies used by many doctors during their clinical management of patients may not necessarily meet the definition of research as well. Given the vague boundary between research and non-research, the PI must ascertain which regulations are applicable and then apply the definitions for research as described above.

When in doubt whether an activity requires DSRB review and approval, the PI may contact the DSRB secretariat and provide a summary of the proposal for a preliminary assessment. Alternatively, the PI may submit an application for the DSRB to review. The DSRB will issue a notification to the PI if the DSRB determines that the proposal does not meet the definition of research.

## **1.6 References and Suggested Readings**

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- a. Singapore Statutes Online, available at <https://sso.agc.gov.sg/>
- b. ICH GCP E6(R2) guidelines, available at <https://www.ich.org/page/efficacy-guidelines>
- c. US Code of Federal Regulations, available at <https://www.govinfo.gov/help/cfr>
- d. Belmont Report, available at <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>
- e. Declaration of Helsinki, available at <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
- f. Bioethics Advisory Committee Singapore, Ethics Guidelines For Human Biomedical Research (2021 Revised Edition) October 2021, available at <https://www.bioethics-singapore.gov.sg/publications/>
- g. Human Biomedical Research (HBRA) Act and subsidiary legislations, available at <https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act>
- h. NHG Research Online Administration and Management Guidebooks on various DSRB-related topics, available at [www.research.nhg.com.sg](http://www.research.nhg.com.sg) > Resources > [ROAM Guidebooks](#)
- i. NHG Proper Conduct of Research Standard Operating Procedures and Templates, available at [www.research.nhg.com.sg](http://www.research.nhg.com.sg) > Resources > [Proper Conduct of Research SOPs & Templates](#)

# **CHAPTER 2**

# **REGULATORY**

# **REQUIREMENTS**

- 2.1 The Human Biomedical Research Act (HBRA)**
- 2.2 The Regulation of Clinical Trials and Clinical Research Materials**
- 2.3 The Personal Data Protection Act (PDPA)**

## **2.1 The Human Biomedical Research Act (HBRA)**

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The HBRA was passed in parliament in August 2015 and is administered by MOH. The Act was introduced to provide a legal framework and clarity in the rapidly rising fields of HBR and the use of human tissue in research as well as establish clear ethical guidelines for the safety and well-being of research subjects.

The Act sets out two separate but related regulatory frameworks:

- a. The Human Biomedical Research Framework; and
- b. The Human Tissue Framework

### **2.1.1 The Human Biomedical Research Framework**

This framework governs HBR with the objective of protecting the rights, safety and welfare of human research participants. It also regulates the conduct of certain types of HBR which are considered more “sensitive” such as research involving human eggs or embryos. These are specified in the Third and Fourth Schedules of The Act.

#### **I. HBR Governance**

The 3 key entities in the HBR framework are:

##### **1. The Research Institution (RI):**

- a. Exercises supervision and control over its researchers who conduct HBR, including supervising and proactively monitoring their research to ensure that they comply with the regulatory requirements and controls; and
- b. Appoints the IRB to review the research proposals of its researchers, and provides the necessary support to ensure the proper functioning of the IRB.

##### **2. The Institutional Review Board (IRB):**

- a. Reviews the research proposals of researchers who come under its appointing RI, assessing (among others) the ethics of the study, the qualifications of the researcher(s), and the adequacy of the monitoring system and safety measures put in place to protect the research subjects; and
- b. Considering the safety and welfare of the research subjects, makes an independent assessment as to whether to approve (or reject) the proposed research.

##### **3. The researcher who conducts HBR:**

- a. Must conduct his research under the supervision and control of a RI;
- b. Must get his research proposal reviewed and approved by an IRB appointed by his RI;
- c. Must ensure that appropriate consent is obtained from each research subject he enrolls in his research; and

- d. In conducting his research, must not deviate from the approved research proposal unless the deviation has also been reviewed and approved by the IRB.

Researchers should be familiar with the requirements of the approving IRB and his/her Research Institution (e.g. minimum training requirements).

## **II. HBR Scope and Definitions**

The scope of HBR that will be regulated under the Act includes two main areas:

1. 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,

And 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.

2. Research that involves –

- a. Human embryos or human gametes; or
- b. Cytoplasmic hybrid embryos; or
- c. The introduction of any human-animal combination embryo into an animal or a 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 development (including a pre-natal animal foetus or animal embryo); or
- e. Any entity created as a result of any process referred to in paragraph (c) or (d).

There is also a limited list of research studies that are excluded from the Act and these are set out in the Second Schedule. Examples of exclusions include human psychological / psychiatric tests, IQ tests as well as clinical trials regulated under the Health Products Act and Medicines Act.

### **III. Requirements for Appropriate Consent and Waivers of Consent**

The Act sets out standards for the consent taking process to ensure that potential subjects of HBR studies are satisfactorily informed and understand their roles in the study. Strict requirements have been put in place for research involving vulnerable populations such as those lacking mental capacity or minors as well as with regards to restricted research set out in the Fourth Schedule.

The IRB also plays a key role in guiding the RI and researchers as to when waivers of consent can be granted under the Act.

*For more information on informed consent requirements and processes, please refer to chapter 5 Informed Consent and chapter 6 Research in Vulnerable Populations.*

### **IV. Special notifications regarding Restricted Human Biomedical Research (rHBR)**

According to HBR 2015, Fourth Schedule, rHBR is defined as:

1. HBR involving human eggs or human embryos.
2. HBR involving:
  - a. The following types of human-animal combination embryos:
    - i. Cytoplasmic hybrid embryos;
    - ii. Human-animal combination embryos created by the incorporation of human stem cells (including induced pluripotent stem cells);
    - iii. Human-animal combination embryos created in-vitro by using —
      - a. Human gametes and animal gametes; or
      - b. One human pronucleus and one animal pronucleus;
      - c. The introduction of human stem cells (including induced pluripotent stem cells) into a prenatal animal foetus or animal embryo;
      - d. The introduction of human pluripotent stem cells (including induced pluripotent stem cells) into a living postnatal animal but excludes the introduction of such human pluripotent stem cells into immunodeficient mice solely for the analysis of teratoma induction;
      - e. The introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into the brain of a living postnatal animal; or
      - f. Any entity created as a result of any process referred to in sub-paragraphs (b), (c) and (d).

Prior to starting a Restricted HBR study

Researchers conducting or intending to conduct rHBR must:

- i. Ascertain if the research study is a rHBR

- ii. Obtain approval from the DSRB and other relevant local regulatory authorities
- iii. Obtain approval from the Ministry of Health (MOH)

### **2.1.2 The Human Tissue Framework (HTF)**

This framework protects the safety and welfare of tissue donors through mechanisms such as mandating informed consent from donors, requiring altruistic donations and ensuring that donors' health and welfare are not jeopardised. This framework also seeks to prohibit the commercial trading of human tissue, regardless of whether or not it is used for the purpose of research.

#### **I. HTF Governance**

Tissue Bank (TB) means an individual or a body of persons, whether corporate or unincorporate, or other organisation, that carries on or conducts any tissue banking activity but excludes an individual, a body of persons or an organisation that conducts any tissue banking activity solely for the purpose of the person's or organisation's own human biomedical research approved or exempted from review by an institutional review board;

Tissue banking activity 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.

The TB is responsible for the supervision and control over its tissue banking activities, including formulating policies and standards, to ensure compliance with regulatory requirements.

#### **II. Scope and Definitions**

Human tissue refers to any human biological material but exclude human biological material specified in the First Schedule of the HBRA. These exclusions include hair shaft, cut without dermal hair root or follicle and naturally excreted bodily fluids such as saliva and sweat.

The key features of this framework include:

##### **1. Prohibition of Commercial Trading of Human Tissue (With effect from 1 January 2017)**

The Act prohibits the commercial trading of human tissue. It is an offence to buy, sell or advertise the buying or selling of human tissue. However, buying and selling of tissue derivatives and tissue products, which are not considered to be 'human tissue', is permissible. These include substantially manipulated tissue and culture expanded cell lines.

## **2. Controls on Removal, Storage, Supply and Use of Human Tissue**

The tissue donor's consent allows the removal, storage, supply and use of his/her tissue in research. The Act explicitly makes it an offence to compel, coerce, intimidate, deceive or mislead a person into giving his tissue.

## **3. Confidentiality of Tissue Donors and Regulation of Tissue Banks**

The Act requires tissue banks to protect the confidentiality of tissue donors and imposes restrictions on disclosure of individually-identifiable information on tissue donors. Tissue banks will also come under the purview of MOH, which will have powers to inspect and audit them to ensure compliance with the regulatory requirements.

### **III. Requirements for Appropriate Consent and Waivers of Consent**

The Act sets out standards for the consent taking process to ensure that potential donors are satisfactorily informed and understand how human tissues donated would be used. Strict requirements have been put in place for donations involving vulnerable populations such as those lacking mental capacity or minors.

#### **2.1.3 References and Further Reading**

For more information on the HBRA and its regulations, please refer to the Ministry of Health website at <https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act>.

## **2.2 The Regulation of Clinical Trials and Clinical Research Materials**

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### **2.2.1 Health Products Act**

The Health Products Act regulates the manufacture, import, supply, presentation and advertisement of health products and of active ingredients used in the manufacture of health products and provide for matters connected therewith. This Act is administered by the HSA.

The First Schedule in the Health Products Act specifies the categories of health products to which the regulatory controls in the Act apply. These health products include:

- Medical devices
- Cosmetic products
- Therapeutic products (more commonly known as chemical and biologic drugs)
- Oral Dental Gums
- Cell, Tissue and Gene Therapy Products (CTGTP)

## **I. Definitions**

**CLINICAL TRIAL** refers to an investigation (of a therapeutic product or Class 2 Cell, Tissue) that involves human subjects, and that is intended to:

- a. Discover or verify its clinical, pharmacological or pharmacodynamics effects;
- b. Identify any adverse effect that may arise from its use;
- c. Study its absorption, distribution, metabolism and excretion; or
- d. Ascertain its safety or efficacy.

**HEALTH PRODUCT** means any substance, preparation or device —

- a. That –
  - i. Is represented for use by humans;
  - ii. Whether because of its presentation or otherwise, is likely to be taken for use by humans; or
  - iii. Is included in a class of substances, preparations or devices which are or are ordinarily intended for use by humans, solely or principally for a health-related purpose; and
- b. That falls within any of the categories of health products specified in the First Schedule of the HPA;

**HEALTH-RELATED PURPOSE** means a therapeutic, preventive, palliative, diagnostic or cosmetic purpose, or any other purpose for the promotion or preservation of human health and well-being, and includes the following:

- a. Preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or the symptoms thereof, in humans;
- b. Compensating for any injury or handicap in humans;
- c. Investigating, modifying or replacing any part of the human anatomy or any physiological process in humans;
- d. Testing the susceptibility of humans to any disease, disorder or ailment;
- e. Influencing, controlling or preventing conception in humans;
- f. Testing for pregnancy in humans;
- g. Inducing anaesthesia in humans;
- h. Destroying or inhibiting micro-organisms that may be harmful to humans; and
- i. Cleansing, fragrancing, deodorising, beautifying, preserving, improving, altering or restoring the complexion, skin, hair, nails or teeth of humans.

**MEDICAL DEVICE** are health products which have a physical or mechanical effect when used on human bodies. These devices are used to:

- Diagnose, alleviate or treat a medical condition, e.g. X-ray machines, contact lenses, prosthetic knee implants
- Measures or monitor functions of the body, e.g. blood pressure or blood sugar monitoring machines

Products used to maintain or support general well-being without specific medical claims such as body toing equipment, magnetic accessories and massages, are not medical devices.

Medical Device means -

- a. Any instrument, apparatus, implement, machine, appliance, implant, reagent for in-vitro use, software, material or other similar or related article that is intended by its manufacturer to be used, whether alone or in combination, for humans for one or more of the specific purposes of —
  - i. Diagnosis, prevention, monitoring, treatment or alleviation of disease;
  - ii. Diagnosis, monitoring, treatment or alleviation of, or compensation for, an injury;
  - iii. Investigation, replacement, modification or support of the anatomy or of a physiological process, mainly for medical purposes;
  - iv. Supporting or sustaining life;
  - v. Control of conception;
  - vi. Disinfection of medical devices; or
  - vii. Providing information by means of in-vitro examination of specimens derived from the human body, for medical or diagnostic purposes, and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means, and which is not a cell, tissue or gene therapy product; and
- b. The following articles:
  - i. Any implant for the modification or fixation of any body part;
  - ii. Any injectable dermal filler or mucous membrane filler;
  - iii. Any instrument, apparatus, implement, machine or appliance intended to be used for the removal or degradation of fat by invasive means.

**THERAPEUTIC PRODUCT** means any substance that –

- a. Is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, including any of the following purposes:
  - i. For preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or any symptom thereof;
  - ii. For investigating, modifying or replacing any physiological process;
  - iii. For influencing, controlling or preventing conception;
  - iv. For inducing anaesthesia;
- b. Has as a constituent any of the following active ingredients:
  - i. Any chemical or botanical element, naturally-occurring chemical or botanical material, or chemical product obtained by chemical change or synthesis;
  - ii. Any metabolite from a micro-organism;
  - iii. Any macromolecule extracted from an organism;
  - iv. Any substance derived from a biological system, including any of the following:
    - A whole cell or micro-organism, such as a whole virus or bacterium used as a vaccine;
    - A part of a micro-organism, such as a sub-unit vaccine;
    - A plasma-derived product;
    - A biotechnology-derived substance, such as a protein or polypeptide, or a recombinant vaccine for a preventive purpose;
- c. Exerts an inherent effect either pharmacologically, chemically or by other physiological means, leading to its use for a therapeutic, preventive, palliative or diagnostic purpose; and
- d. Is not any of the following:
  - i. A medical device;
  - ii. A cell, tissue or gene therapy product;
  - iii. Whole blood or any blood component;
  - iv. Any Chinese proprietary medicine;

- v. Any homoeopathic medicine;
- vi. Any medicated oil or balm;
- vii. Any quasi-medicinal product;
- viii. Any traditional medicine.

**CELL, TISSUE or GENE THERAPY PRODUCT (CTGTP)** means any substance that —

- a. Is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, including any of the following purposes:
  - i. For preventing, diagnosing, treating, curing or alleviating any disease, disorder, injury, ailment, handicap or abnormal physical or mental state, or any symptom thereof;
  - ii. For replacing, repairing, regenerating or reconstructing any anatomy, or for modifying or replacing any physiological process;
  - iii. For regulating, repairing, replacing, adding or deleting a genetic sequence or modifying genetic material;
  - iv. For supporting or sustaining life;
- b. Has as a constituent any of the following substances or combination of substances:
  - i. Viable or non-viable human cells or tissues;
  - ii. Viable animal cells or tissues;
  - iii. Recombinant nucleic acids, where the effect of the recombinant nucleic acid relates directly to the recombinant nucleic acid sequence that it contains or to the product of the genetic expression of its sequence;
- c. Achieves its primary intended action by pharmacological, immunological, physiological, metabolic or physical means, leading to its use for a therapeutic, preventive, palliative or diagnostic purpose; and
- d. Is not any of the following:
  - i. A recombinant vaccine for a preventive purpose;
  - ii. An in-vitro diagnostic product;
  - iii. Bone marrow, peripheral blood or umbilical or placental cord blood from a human that is minimally manipulated and intended for homologous use;

- iv. Cells and tissues obtained from a patient that are minimally manipulated and re-implanted for homologous use into the same patient during the same surgical procedure;
- v. Organs and tissues that are minimally manipulated and intended for transplant;
- vi. Reproductive cells (sperm, eggs) and embryos intended for assisted reproduction;
- vii. Whole blood and any blood component that is minimally manipulated and intended for treating blood loss or blood disorders.

**CLASS 1 CTGT PRODUCT** means a CTGT product that —

- a. Is the result of only minimal manipulation of human cell or tissue;
- b. Is intended for homologous use;
- c. Is not combined or used with —
  - i. a health product categorised as a therapeutic product in the First Schedule to HPA; or
  - ii. a health product categorised as a medical device in the First Schedule to the HPA; and
- d. Is assigned by the Authority as a Class 1 CTGT product due to a lower health risk to a user of the product.

**CLASS 2 CTGT PRODUCT** means a CTGT product other than a Class 1 CTGT product.

## II. Clinical Trials of Therapeutic Products and Applicable CTGTPs

Clinical trials of therapeutic products and applicable CTGTPs (i.e. Class 2 CTGTPs) are regulated under the Health Products (Clinical Trials) Regulations. To conduct clinical trials of therapeutic products and applicable CTGTPs in Singapore, a CTA or CTN issued by HSA will be required. Tables 2 and 3 below outline the various criteria and characteristics of CTA and CTN applications.

Table 2: Criteria to determine if a clinical trial requires a CTA or CTN:

Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)
For clinical trials involving: <ul style="list-style-type: none"> <li>▪ Locally unregistered therapeutic products or Class 2 CTGTPs.</li> <li>▪ Locally registered therapeutic products or Class 2 CTGTPs not used in accordance with product registration*.</li> </ul>	For clinical trials involving: <ul style="list-style-type: none"> <li>▪ Locally registered therapeutic products or Class 2 CTGTPs used in accordance with product registration.</li> </ul>

<ul style="list-style-type: none"> <li>▪ Healthy volunteers (unless approved population is healthy individuals, e.g. vaccines).</li> </ul> <p><i>*Used for a different indication, patient population, dosing regimen, dosage form, etc. from the approved label.</i></p>	
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Table 3: Key differences between CTA and CTN applications

	Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)
<b>Risk level of clinical trial</b>	“Higher risk” trials	“Lower risk” trials
<b>DSRB and HSA submission timelines</b>	Applications to HSA and DSRB may be submitted concurrently	Applications to HSA can only be submitted after obtaining DSRB approval
<b>HSA review timeline</b>	30 working days, or 15 working days for Phase 1 trials solely to evaluate bioequivalence, bioavailability, food effect or drug-drug interactions. 60 working days for Class 2 CTGTP trials.	5 working days

CTA and CTN are valid throughout the duration of the study.

Class 1 CTGTP trials are required to comply with the requirements of the Human Biomedical Research Act (HBRA).

### III. Clinical Trials of Medical Devices

Although the sale and supply of medical devices are regulated under the Health Products Act, the conduct of clinical trials of medical devices are not regulated by HSA. Nonetheless, general regulatory controls apply to the use of medical devices in clinical trials [under Health Products (Medical Device) Regulations] and research conduct should comply with Human Biomedical Research Act (HBRA).

#### 2.2.2 Medicines Act

The regulatory controls in the Medicines Act apply to medicinal products such as Chinese proprietary medicines, traditional medicines, homoeopathic medicines and quasi medicinal products (e.g. health supplements).

## **I. Definitions**

**CLINICAL TRIAL** refers to an investigation or series of investigations consisting of the administration of one or more medicinal products of a particular description by, or under the direction of —

- a. A doctor or dentist to one or more of his patients; or
- b. Two or more doctors or dentists, each product being administered by or under the direction of one or other of those doctors or dentists to one or more of his patients, where there is evidence that medicinal products of that description have effects which may be beneficial to the patient or patients in question and the administration of the product or products is for the purpose of ascertaining whether, or to what extent the product has, or the products have, those or any other effects, whether beneficial or harmful.

**MEDICINAL PRODUCT** means any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, supplied, imported or exported for use wholly or mainly in either or both of the following ways:

- a. Use by being administered to one or more human beings or animals for a medicinal purpose;
- b. Use as an ingredient in the preparation of a substance or article which is to be administered to one or more human beings or animals for a medicinal purpose.

**MEDICINAL PURPOSE** means any one or more of the following purposes:

- a. Treating or preventing disease;
- b. Diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;
- c. Contraception;
- d. Inducing anaesthesia;
- e. Otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way.

## **II. Clinical Trials of Medicinal Products**

Clinical trials of medicinal products are regulated under the Medicines (Clinical Trials) Regulations. These include clinical trials investigating medicinal products such as Chinese proprietary medicines, traditional medicines, homoeopathic medicines and quasi medicinal products (e.g. health supplements).

To conduct clinical trials of medicinal products in Singapore, a CTC from HSA will be required. Table 4 below outline the criteria and process for CTC applications.

*Table 4: Criteria and Process for CTC Applications*

Clinical Trial Certificate (CTC) Applications	
<b>Registration status of medicinal product(s)</b>	All clinical trials investigating medicinal product(s) will require a CTC, regardless of the local registration status of the medicinal product(s).
<b>Risk level of clinical trial</b>	All risk levels
<b>DSRB and HSA submission timelines</b>	Applications to HSA and DSRB may be submitted concurrently.
<b>HSA review timeline</b>	30 working days

## 2.2.4 Observational Clinical Trials

OBSERVATIONAL TRIAL is a research study where:

- a. The product is prescribed by a locally registered doctor / dentist to a patient in the usual manner in accordance with the terms of the product registration or product licence;
- b. The decision to prescribe the product to the patient is clearly separated from the decision to include the patient in the trial;
- c. The assignment of any patient involved in the trial to a particular therapeutic strategy in which the product is used is not decided in advance by a protocol but falls within the current practice of the locally registered doctor / dentist carrying out the trial.

Observational trials are excluded from the regulatory controls under the Health Products Act and Medicines Act. However, such trials such comply with requirements of Human Biomedical Research Act (HBRA).

## 2.2.5 Clinical Research Materials (CRM)

Clinical Research Materials (CRM) refer to any registered or unregistered **therapeutic product**, **medicinal product**, **medical device**, applicable cell, tissue and gene therapy product (**CTGTP**) or **placebo**, that is manufactured, imported or supplied for the purpose of being used in clinical research\*, by way of administration to a trial participant in accordance with the research protocol or for a clinical purpose.

*\*Clinical research refers to any research involving human subjects, and is a collective term comprising clinical trials regulated by HSA as well as clinical research studies not regulated by HSA (e.g. HBRA regulated studies).*

**Regardless of whether HSA regulates the research study**, the manufacture, import and supply of CRM in Singapore must comply with the respective regulatory controls for CRM as per below (Table 5):

Table 5: Applicable regulations for CRM

Clinical Research Material	Applicable Regulations
▪ Therapeutic products ▪ Class 2 CTGTPs ▪ Class 1 CTGTPs for which the manufacturer / importer / wholesaler notification has not been made to HSA.	Health Products (Clinical Research Materials) Regulations
Medicinal products	Medicines (Medicinal Products as Clinical Research Materials) Regulations
Medical devices	Health Products (Medical Devices) Regulations

## I. CRM Notification to HSA

A CRM notification must be submitted to HSA prior to the following:

- Import of any CRM for local clinical research use.
- Supply by the local manufacturer of CRM for local clinical research use, including CRM compounded at the local trial site.

CRM notification is not required for the following:

- Locally registered CRM obtained from local commercial sources
- Import of locally registered CRM for local clinical research use if the importer already has a valid importer's license for the import of CRM
- Supply of a locally registered CRM by its local manufacturer for local clinical research use if the manufacturer has a valid manufacturer's license
- Supply of CRM by a local manufacturer if the manufacture of the CRM being supplied comprises solely of the packaging or labelling of the CRM
- Import of a minimally manipulated CTGTP CRM for local clinical research use by a known importer
- Supply of a minimally manipulated CTGTP CRM by its known manufacturer for local clinical research use

## II. Duties and Obligations of CRM Dealers

All parties involved in supplying CRM – including local manufacturers, importers, suppliers and sponsors – must comply with the following duties and obligations relating to CRM.

Table 6: Duties and obligations of parties involved in supplying CRM other than medical device CRM.

Duties and Obligations	Parties			
	Local Manufacturer	Importer	Supplier	Sponsor
<b>All CRM (including locally-registered products)</b>				
Maintain records of receipt and supply	✓*	✓*	✓	✓*
Ensure compliance with labeling requirements	✓*	✓*	✓	✓*
Report unexpected serious adverse drug reactions (USADR) to HSA	-	-	-	✓
Establish and maintain a system of traceability (only for CRM that is a CTGTP)	✓	✓	✓	✓*
Report CRM defects	✓	✓	✓	✓*
Notify HSA 24 hours before recall of CRM	✓	✓	✓	✓*
<b>Additional requirements for locally manufactured or imported CRM</b>				
Ensure the CRM (TP/MP) is of the correct identity and conforms with the applicable standards of strength, quality and purity for the material	✓	✓	-	-
Maintain records of manufacture, assembly and testing	✓	-	-	-
Ensure CRM supply / use only for clinical research purposes	✓*	✓*	✓	✓*
Ensure CRM use only in IRB-approved clinical research	-	-	-	✓
Ensure disposal / export of CRM within 6 months after research completion/ termination	-	-	-	✓
Maintain records of disposal / export of CRM	-	-	-	✓

\*Responsibility as “Supplier”; includes local manufacturer, importer, wholesaler, sponsor, investigator where applicable, if the party involved in the activity of supplying a TP/CTGTP as CRM). This is also applicable to TP, CTGTP and MP used in clinical research that is not regulated by HSA.

Table 7: Duties and obligations of parties involved in supplying medical device for clinical research purposes

Duties and Obligations	Parties			
	Local Manufacturer	Importer	Supplier*	Sponsor
<b>All CRM (including locally-registered products)</b>				
Ensure the CRM (MD) complies with “Safety and Performance Requirements for Medical Devices” in the First Schedule of the Health Products (Medical Devices) Regulations	✓	✓	-	-
Maintain records of manufacture, assembly and testing	✓	-	-	-
Maintain records of receipt and supply	✓*	✓*	✓	✓*
Ensure compliance with labeling requirements	✓	✓	✓	✓*
Report MD defects and adverse effects to HSA	✓	✓	✓	✓*
Maintain records of complaints	✓	✓	✓	✓*
Notify HSA concerning recall	✓	✓	✓	✓*
Notify HSA concerning field safety corrective actions	✓	✓	✓	✓*
<b>Additional requirements for locally manufactured or imported CRM</b>				
Ensure CRM supply / use only for clinical research purposes	✓*	✓*	✓	✓*
Ensure CRM use only in IRB-approved clinical research	-	-	-	✓
Ensure disposal / export of CRM within 6 months of research completion/ termination	-	-	-	✓
Maintain records of disposal / export	-	-	-	✓

\*Responsibility as “Supplier”; includes local manufacturer, importer, wholesaler, sponsor, investigator, where applicable, if the party is involved in the activity of supplying a MD for clinical research.

### III. Record Keeping for CRM

The CRM regulations require designated parties to maintain records of manufacture, receipt, supply and disposal of CRM.

Record-keeping for CRM other than medical device CRM must comply with the following requirements.

Table 8: Requirements for record-keeping in relation to CRM other than medical device CRM

This is applicable to any supplier of CRM other than medical device CRM, including; importers; local manufacturers; wholesaler (e.g. distributor), sponsor, investigator or other healthcare professional (e.g. pharmacist) supplying CRM.

	Type of Records		
	Manufacture	Receipt and Supply	Disposal (Including Export or Putting to Other Use)
<b>Applies to</b>	Locally-manufactured CRM (other than medical device CRM)	All CRM (other than medical device CRM)	Unused CRM (including expired CRM or those which can no longer be used for research) that was imported or locally manufactured is disposed of (e.g. sent for destruction) or exported within 6 months of the conclusion/ termination of the clinical research
<b>Party Responsible</b>	Manufacturer	Any person who supplies CRM, including the importers, local manufacturers, wholesaler (e.g. distributor), sponsor, investigator or other healthcare professionals (e.g. pharmacist).	Sponsor
<b>Required Elements in Records</b>  <i>NB: The records must be kept up-to-date at all times and be available for inspection by HSA upon request.</i>	All records of the manufacture, assembly and testing of the material, and, records of traceability (for CRM that is a CTGTP).	<ul style="list-style-type: none"> <li>• Proprietary name (i.e brand name) or other description</li> <li>• Identification number of the CRM (e.g. control number, lot/ batch number)</li> <li>• Details of each receipt or supply, including:               <ul style="list-style-type: none"> <li>- Date on which the CRM was received/ supplied;</li> <li>- Quantity of CRM received/ supplied, and</li> <li>- Name and address of the person from</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Proprietary name (i.e brand name) or other description</li> <li>• Identification number of the CRM (e.g. control number, lot/ batch number)</li> <li>• Details of the disposal, export or putting to some other use, including</li> <li>• The date on which the CRM was disposed, exported or put to some other use,</li> </ul>

		<p>whom the CRM was received or to whom the CRM will be supplied.</p> <ul style="list-style-type: none"> <li>• The quality of CRM disposed, exported or put to some other use, and</li> <li>• The name and address of the person responsible for the disposal, export or putting to some other use of the CRM.</li> </ul>	
<b>Duration of Record-Keeping</b>	<p><u>For registered &amp; unregistered investigational CRM &amp; unregistered auxiliary CRM:</u></p> <ul style="list-style-type: none"> <li>• 5 years after completion/ discontinuation of the last clinical trial in which the batch was used</li> </ul> <p><u>For registered auxiliary CRM, the longer of the following periods:</u></p> <ul style="list-style-type: none"> <li>• 1 year after the expiry date of the material; or</li> <li>• 5 years after the date of such manufacturer, assembly and testing; and</li> </ul> <p><u>For traceability records relating to CTGTP CRM:</u></p>	<p>For CRM supplied for use in a <u>regulated clinical trial</u> (whichever is the latest):</p> <ul style="list-style-type: none"> <li>• No more pending or planned applications for registration of the TP, CTGTP or MP that was tested in the clinical trial / research</li> <li>• 2 years after the last of such registrations has been granted</li> <li>• 2 years after HSA was informed of the termination of the clinical trial</li> <li>• 6 years after completion of clinical trial (i.e. 6 years after "Last-Patient-Last-Visit") <ul style="list-style-type: none"> <li>- If the clinical trial involves an applicable CTGTP and in the case of a record that relates to the traceability of the product, 30 years after the expiry date of that product or any other shorter period that HSA allows in a particular case;</li> </ul> </li> <li>• Any other period as directed by HSA.</li> </ul> <p>For CRM supplied for use in a clinical research that is <u>not regulated</u> by HSA:</p> <ul style="list-style-type: none"> <li>• If the CRM is not a CTGTP - 2 years after the supply;</li> <li>• If the CRM is a CTGTP and; <ul style="list-style-type: none"> <li>- The records do not relate to traceability, 2 years after the supply; or</li> <li>- The records relate to traceability, 30 years after the expiry date of the CTGTP, or any</li> </ul> </li> </ul>	

	<ul style="list-style-type: none"> <li>• 30 years after expiry date of the product or any other shorter period that HSA allows in a particular case.</li> </ul>	other shorter period that HSA allows in a particular case;
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*There are additional record-keeping requirements if the clinical research material is a Pharmacy-Only (P) Medicine or a Prescription-only medicine (POM) that is supplied directly to the trial participant, such as in a retail pharmacy setting.*

Table 9: Requirements for record-keeping in relation to medical devices (MD) as CRM

	Type of Records		
	Manufacture	Receipt and/or Supply	Disposal (Including Export or Putting to Other Use)
<b>Applies to</b>	Locally-manufactured MD as CRM	All MD CRM	Imported or locally manufactured MD CRM
<b>Party Responsible</b>	Manufacturer	Any person who supplies MDs as CRM, including the manufacturers, importers, wholesalers, sponsors.	Sponsor
<b>Required Elements in Records</b> <i>NB: The records must be kept up-to-date at all times and be available for inspection by HSA upon request.</i>	As required by existing Health Products (Medical Device) Regulations	<ul style="list-style-type: none"> <li>• Proprietary name (i.e. brand name) or other description of the CRM</li> <li>• Identification number or mark of the CRM (e.g. control number, lot number, batch number, serial number)</li> <li>• Details of each receipt or including:               <ul style="list-style-type: none"> <li>- Date on which the CRM was received or supplied;</li> <li>- Quantity of CRM received or supplied, and</li> <li>- Name and address of person from whom the CRM was received or to</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Proprietary name (i.e. brand name) or other description of the MD CRM</li> <li>• Identification number or mark of the CRM (e.g. control number, lot number, batch number, serial number)</li> <li>• Details of the disposal, export or putting to some other use including:               <ul style="list-style-type: none"> <li>- Date on which the CRM was disposed, export or put to some other use,</li> </ul> </li> </ul>

		<p>whom the CRM will be supplied.</p>	<ul style="list-style-type: none"> <li>- Quantity of CRM disposed, export or put to some other use, and</li> <li>- Name and address of person responsible for the disposal, export or putting to some other use of the CRM.</li> </ul> <p>The Sponsor must obtain permission from HSA for any unused CRM deems as fit to be put to some other use other than in clinical research before using for that purpose. If permission is granted by HSA for the unused MD CRM to be used for that purpose, the MD will no longer be considered a CRM but is still subject to applicable laws relating to medical devices including the Health Products (Medical Device) Regulations.</p>
<b>Duration of Record-Keeping</b>	<ul style="list-style-type: none"> <li>• Projected useful life of the MD; or</li> <li>• 2 years after the MD is supplied (Whichever is longer)</li> </ul>	<p>For <u>unregistered</u> MD CRM supplied for use in a <u>regulated clinical trial</u> (whichever is the latest):</p> <ul style="list-style-type: none"> <li>• No more pending or planned applications for registration of the TP/ MP that was tested in the clinical trial/ research</li> <li>• 2 years after the last of such registrations have been granted</li> </ul>	<p>For <u>unregistered</u> MD CRM supplied for use in a <u>regulated clinical trial</u> (whichever is the latest):</p> <ul style="list-style-type: none"> <li>• No more pending or planned applications for registration of the TP/ MP that was tested in the clinical trial/ research</li> </ul>

	<ul style="list-style-type: none"> <li>• 2 years after HSA was informed of termination of the clinical trial</li> <li>• 6 years after completion of clinical trial (i.e. 6 years after "Last-Patient-Last-Visit), or</li> <li>• Any other period as directed by HSA</li> </ul> <p>MD CRM (whether registered or unregistered) is supplied for used in clinical research <u>not regulated</u> by HSA, or if the MD CRM is a registered MD, records of receipt and supply must be kept for either:</p> <ul style="list-style-type: none"> <li>• The projected useful life of the medical device, or</li> <li>• 2 years after the date on which the medical device was supplied, whichever is the longer period</li> </ul>	<ul style="list-style-type: none"> <li>• 2 years after the last of such registrations have been granted</li> <li>• 2 years after HSA was informed of termination of the clinical trial</li> <li>• 6 years after completion of clinical trial (i.e. 6 years after "Last-Patient-Last-Visit), or</li> <li>• Any other period as directed by HSA</li> </ul> <p>If the MD CRM (whether registered or unregistered) is supplied for used in clinical research <u>not regulated</u> by HSA, or if the MD CRM is a registered MD, records of disposal must be kept for 2 years after the time when the medical device is put to some other use, dispose of or exported.</p>
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## 2.2.6 References and Further Reading

For more information on the regulatory requirements for clinical trials and clinical research materials, please refer to the following websites:

- Singapore Statutes Online, available at <https://sso.agc.gov.sg>.
- Health Sciences Authority website, available at <https://www.hsa.gov.sg>.

## 2.3 The Personal Data Protection Act (PDPA)

The purpose of the PDPA is to govern the collection, use and disclosure of personal data by organisations in a manner that recognises both the right of individuals to protect their personal data, and the need of organisations to collect, use or disclose personal data for purposes that a reasonable person would consider appropriate in the circumstances.

## **Scope and Definitions**

**PERSONAL DATA** refers to data, whether true or not, about an individual who can be identified from that data; or from that data and other information to which the organisation has or is likely to have access.

- This includes unique identifiers (e.g. NRIC number, passport number), as well as any set of data (e.g. full name, date of birth, full address etc.) which when taken together would be able to identify the individual.

Researchers should note that the scope of PDPA only applies to identifiable data. The PDPA does not apply to data that is used in anonymised form.

The PDPA takes into account the following concepts:

- Consent – organisations may collect, use or disclose personal data only with the individual's knowledge and consent (with some exceptions);
- Purpose – organisations may collect, use or disclose personal data in an appropriate manner for the circumstances, and only if they have informed the individual of purposes for the collection, use or disclosure; and
- Reasonableness – organisations may collect, use or disclose personal data only for purposes that would be considered appropriate to a reasonable person in the given circumstances.

### **2.3.1 Data Protection Obligations under PDPA**

#### **1. Accountability Obligation**

- To undertake measure to ensure that organization meet their obligations under the PDPA such as making information about your data protection policies, practices and complaints process available upon request and designating a data protection officer (DPO) and making the business contact information available to the public.

#### **2. Notification Obligation**

- To notify individuals of the purposes for which your organization is intending to collect, use or disclose their personal data.

#### **3. Consent Obligation**

- To only collect, use or disclose personal data for purposes which an individual has given his/her consent to.
- To allow the individual to withdraw consent, with reasonable notice, and inform him/her of the likely consequences of withdrawal. Once consent is withdrawn, make sure that you cease to collect, use or disclose the individual's data.

#### **4. Purpose Limitation Obligation**

- To only collect, use or disclose personal data for the purposes that a reasonable person would consider appropriate under the given circumstances and for which the individual has given consent.
- An organization may not, as a condition of providing a product or service, require the individual to consent to the collection, use or disclosure of his or her personal data beyond what is reasonable to provide that product or service.

#### **5. Accuracy Obligation**

- To make reasonable effort to ensure that personal data collected by is accurate and complete, if it is likely to be used to make a decision that affects the individual, or to be disclosed to another organisation.

#### **6. Protection Obligation**

- To ensure reasonable security arrangements have been made to protect the personal data in your organisation's possesses to prevent unauthorised access, collection, use, disclosure or similar risks.

#### **7. Retention Limitation Obligation**

- To cease retention of personal data or dispose of it in a proper manner when it is no longer needed for any business or legal purpose.

#### **8. Transfer Limitation Obligation**

- Transfer personal data to another country only according to the requirements prescribed under the regulations, to ensure that the standard of protection is comparable to the protection under the PDPA, unless exempted by the PDPC.

#### **9. Access and Correction Obligation**

- Upon request, organisations have to provide individuals with access to their personal data as well as information about how the data was used or disclosed within a year before the request.
- Organisation are also required to correct any error or omission in an individual's personal data as soon as practicable and send the corrected data to other organisations to which the personal data was disclosed (or to selected organization that the individuals has consent to), within a year before the correction is made.

#### **10. Data Breach Notification Obligation**

- In the event of a data breach, organisations must take steps to access if it is notifiable. If the data breach likely results in significant harm to individuals, and/or are of significant scale, organisations are required to notify the PDPC and the affected individuals as soon as practicable.

## **11. Data Portability Obligation**

- At the request of the individual, organization are required to transmit the individual's data that is in the organisations' possession or under its control, to another organization in a commonly used machine-readable format.

Exception may apply to the obligations above. For more information, please refer to Advisory Guidelines on Key Concepts in the Personal Data Protection Act.

### **2.3.2 Collection, use and disclosure of personal data without consent**

Please refer to Second, Third and Fourth Schedule of the PDPA for more information.

### **2.3.3 References and Further Reading**

For more information on the PDPA, please refer to the following websites:

- Singapore Statutes Online, available at <https://sso.agc.gov.sg>
- Personal Data Protection Commission Singapore, Data Protection Obligations, available at <https://www.pdpc.gov.sg>

# **CHAPTER 3**

# **THE STUDY TEAM**

- 3.1 Who Can Be a Principal Investigator (PI)?**
- 3.2 Minimum Training Requirements for Investigators and Study Team Members**
- 3.3 Responsibilities of a PI**
- 3.4 Change of PI and / or Study Team Members**
- 3.5 Financial Conflict of Interest (FCOI)**
- 3.6 Institutional Conflict of Interest (ICOI)**

## **3.1 Who Can Be A Principal Investigator (PI)?**

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### **3.1.1 Minimum Qualifications to be a PI**

The minimum requirements for being a PI of a research study is based on the risks involved in the research study.

MINIMAL RISK under the Human Biomedical Research Act Section 1(2) means the probability and magnitude of harm and discomfort anticipated in the research or removal human tissue that are not greater, in and of themselves than those ordinarily encountered (a) in the daily life of normal and healthy persons; or (b) during the performance of routine physical or psychological examinations or tests.

Minimal risk studies – Research proposals that qualify for Exempt / Expedited review will be considered minimal risk studies. To be a PI for a minimal risk study, the individual should at least be:

- a. Doctors - Fully registered medical practitioner, or a level 2 conditionally registered medical practitioner (please refer to subsequent section on “Special Considerations”)
- b. Dentists - Fully registered/ conditionally registered/ temporarily registered dentists
- c. Nurses - Registered nurse
- d. Allied Health Staff – Registered allied health practitioner
- e. Case managers, research scientists, research fellows and health services research staff, or as determined to be eligible by the DSRB

For registered pharmacists to be a PI for minimal risk HSA-regulated clinical trials and other clinical research, the following requirements should be met:

- (a) The research involves locally registered products;
- (b) The PI must have a PhD and/or PharmD and/or other appropriate Postgraduate Qualification, hold a primary appointment in a local institution and salaried by the institution, with a demonstrated track record of research for example, as evidenced by the award of nationally competitive funding, substantial publication record or a laboratory or clinical research program that carries out research in Singapore; and
- (c) For interventional clinical trials, a locally-registered physician(s) should be involved as co-investigator(s) to provide direct medical supervision and monitoring of the trial subjects.

Greater than minimal risk studies – Research proposals that do not qualify for Exempt / Expedited review and are reviewed by the Full Board are considered to be greater than minimal risk. To be a PI for a greater than minimal risk study that is not a HSA regulated, the individual should at least be:

- a. Doctors – Fully registered Associate Consultant and above, or who is a level 3 conditionally registered Associate Consultant and above (please refer to subsequent section on “Special Considerations”);
- b. Dentists – Fully registered/ conditionally registered/ temporarily registered Associate Consultant and above.
- c. Nurses – Senior Staff Nurse (SSN) – Must have an Associate Consultant and above on the research team.
- d. Allied health staff - Senior therapist / pharmacist, with a member of the research team who must be an Associate Consultant and above.

For clinical trials and other clinical research that are HSA regulated, the PI should be a locally registered doctor who is a Fully Registered Associate Consultant and above, or a level 3 Conditional Registered Associate Consultant and above, or a locally registered dentist who is a Fully Registered/ Conditionally Registered/ Temporarily Registered Associate Consultant and above.

For research conducted in institutions under the oversight of NHG DSRB, the PI should be a staff of NHG or the partner institutions. This requirement is not solely for the purpose of the application to DSRB, as the PI has the responsibility for ensuring that the conduct of the research is in compliance with ICH GCP and all other applicable guidelines and regulations.

### **3.1.2 Special Considerations**

#### **I. Visiting Consultants**

If the PI holds a Visiting Consultant position within NHG or partner institutions, there should be at least one full time staff within the institution who is a part of the study team for that study (the designation of the study team member should follow the requirement guideline under 3.1.1 and 3.1.2). The Visiting Consultant may not be PIs of studies unless the NHG or partner institutions have given their approval for the Visiting Consultant to conduct studies in their respective institutions.

#### **II. Conditionally Registered Medical Practitioners**

- A level 2 conditionally registered medical practitioner is one who has fulfilled 0.5 years of practice at level 1 and has received at least an “above average” performance grading for the past 6 months.
- A level 3 conditionally registered medical practitioner is one who has fulfilled 0.5 years of practice at level 1 and has received at least an “above average” performance grading for level 1, as well as fulfilled 1.0 year of practice at level 2 and has been ascertained to be ready to work independently, but has yet to fulfil the specified period of supervised practice required for computation towards full registration.

The following set of conditions must be fulfilled before a level 2 or level 3 conditionally registered medical practitioner may be accepted as PI of a study:

- a. The supervisor of the level 2 or level 3 practitioner must declare in writing that:
  - i. He / She is aware of, and supports, the involvement of the conditionally registered doctor as PI;
  - ii. He / She will provide guidance and include research activities in regular progress reports to the Singapore Medical Council (SMC); and
  - iii. Based on the doctor's current progress and technical and ethical competency, the conditionally registered doctor is deemed competent to assume the role of PI, and affirms that the conditionally registered doctor has adequate medical expertise to provide medical care and decisions for the safety and welfare of subjects.
- b. The conditionally registered doctor declares that his/ her involvement in research as PI has been provided to SMC and no objection has been received from SMC.
- c. The DR and IR / Institutional Officer (IO) approve of the conditionally registered doctor to be the PI of the study.

### **III. Conditionally/ Temporarily Registered Dentists**

For a conditionally/ temporarily registered dentist to be accepted as a PI for a study; the following conditions must be fulfilled:

- a) The supervisor of the dentist must declare in writing that:
  - i. He/ she is aware of, and supports, the involvement of the conditionally/ temporarily registered dentist as PI;
  - ii. He/ she will provide guidance and include research activities in regular progress reports to Singapore Dental Council (SDC); and
  - iii. Based on the conditionally/ temporarily registered dentist's current progress and technical and ethical competency, the conditionally/ temporarily registered dentist has adequate dental expertise to provide clinical care and make clinical decisions for the safety and welfare of the subjects.
- b) The conditionally/ temporarily registered dentist declares that his/ her involvement in research and PI has been provided to SDC and no objection has been received from SDC.
- c) The DR and IR/ IO approve of the conditionally temporarily registered dentist to be the PI of the study.

#### **IV. Multi-Cluster Studies**

For cross-cluster research studies such as between NHG/ NHG-partner institutions and SingHealth / SingHealth-partner institutions, the IRB application can be submitted to either SingHealth CIRB or NHG DSRB, depending on the overall PI's cluster. Some examples are highlighted below:

- If the study is a grant-awarded study, the overall PI would be the person who is awarded the grant, and the application should be submitted to his / her cluster's IRB.
- If the study is an industry- or commercially-sponsored study, an overall PI would have to be selected and the application submitted to his / her cluster's IRB.
- If the study is an investigator-initiated (with no grant or funding required), the overall PI would be the person who initiated the study. The application should be submitted to his / her cluster's IRB.
- If the research project involves different clusters, and the overall PI for the research project is not from NHG or partner institutions; it would be necessary to have a Site PI from NHG or partner institution.

*For more information on the submission and review of cross-cluster applications, please refer to section 4.1.5 and 4.1.6.*

#### **V. Multi-Centre Studies Within NHG and Partner Institutions**

If the research study is going to be conducted in more than one site within NHG and / or partner institutions, the PI for one of the sites should be the submitting PI for the study for the purposes of communication with the DSRB. The rest of the PIs may be listed as site PIs. The site PIs does not relinquish their responsibility for the study at their respective institutions.

*For more information on Who Can be a Principal Investigator, please refer to <https://www.research.nhg.com.sg> > Conducting Research > Who can be a Principal Investigator.*

### **3.2 Minimum Training Requirements for Investigators and Study Team Members**

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The intent of having minimum training requirements is for investigators and study team members involved in the design, conduct and reporting of research to appreciate and apply the underlying ethical principles to their day-to-day research practice.

The PI and delegated study team member(s) should meet the minimum training requirements set by the reviewing IRB and the Research Institution, and be adequately trained on all delegated study tasks (e.g. protocol / study specific training) prior to performing any study procedure.

The documentation of completed trainings (i.e. protocol/ study specific training) for all study team members, including PI and new study team member(s) should be documented and filed in the investigator file. Other additional relevant training(s) or certification(s) for study team member(s) (e.g. phlebotomy course) should also be kept in the investigator file.

### **3.2.1 Training Courses**

The minimum training requirements comprise of **4** types of trainings:

- I. Collaborative Institutional Training Initiative (CITI);
- II. Good Clinical Practice (GCP) course;
- III. Financial conflict of interest (FCOI) training;
- IV. Research Institution (RI) Specific Training Minimum Requirements (e.g. HBRA training)

Each of these trainings is described below in more detail.

#### **I. Collaborative Institutional Training Initiative (CITI) – The protection of human research subjects training programme**

CITI is a web-based training programme covering various foundational topics on ethical research and human protection. The CITI program is available online at <https://www.citiprogram.org.>

All PI(s), Site PIs and Co-Is of research conducted within NHG and partner institutions are required to complete the CITI Program's Investigator's Course.

When setting up the CITI account, PI and study team member must select that they are affiliated to "National Healthcare Group – Singapore" in order to access the correct curriculum. Study team should select the appropriate modules within CITI to read according to the type of research study(ies) that they are intending to conduct.

1. Investigators conducting biomedical research (i.e. making submissions to DSRB domains A to E) are required to complete the following modules:

a. 10 core modules (listed in table 10 below), comprising 7 fundamental research ethics modules and 3 NHG-specific modules:

*Table 10: CITI core modules*

<b>Module Type</b>	<b>Module Title</b>
Research ethics modules	Belmont Report and CITI Course Introduction
	History and Ethics of Human Subject Research
	Informed Consent
	Social and Behavioural Research (SBR) for Biomedical Researchers

	Records-Based Research
	Populations in Research Requiring Additional Considerations and/or Protections
	Conflicts of Interest in Research Involving Humans**
NHG-specific modules	NHG-Singapore. Overview of Domain Specific Review Board (DSRB) Review Process**
	NHG-Singapore. Overview of the Regulatory Framework and Guidelines in Singapore
	National Healthcare Group – Singapore

\*\* These two core modules also constitute the NHG FCOI training requirements. Please see section 3.2.1.3 below for more details.

- b. 5 elective modules, selected from the available list of elective modules. Modules may be selected based on investigators' area(s) of specialty, relevance to the study(ies) being conducted and/or individual interest.
2. Investigators conducting population health research (i.e. making submissions to DSRB domain F) are required to complete the following modules:
- a. 10 core modules (as listed in table 10 above), comprising 7 fundamental research ethics modules and 3 NHG-specific modules.
  - b. 5 elective modules, selected from the available list of Social, Behavioural and Educational (SBE)-related elective modules. These modules may be identified by the "SBE" suffix in their names. Modules may be selected based on investigators' area(s) of specialty, relevance to the study(ies) being conducted and / or individual interest.

## II. Good Clinical Practice (GCP) Course

Based on the ICH GCP E6(R2) guidelines and incorporating local regulatory requirements, the GCP course seeks to equip subjects with basic knowledge and understanding of how GCP principles may be applied to the conduct of clinical trials. Experienced speakers from various clinical research-related sectors will deliver a series of lectures covering the following broad elements:

- Core principles of GCP and ethical research;
- Local regulatory requirements and legal framework for clinical trials;
- Responsibilities of the sponsor and investigator;
- Procedures related to the operationalization and conduct of clinical trials.

The GCP course is administered by the NHG Group Research, and is available in both online and classroom formats.

GCP certification is mandatory for PIs and site PIs conducting clinical trials regulated by HSA within NHG and partner institutions.

### **III. Financial Conflict of Interest (FCOI) Training Requirements**

The FCOI training requirements aim to educate researchers on how conflicting interests may adversely affect the protection of subjects or the credibility of the human research protection programme. All investigators and study team members, who are involved in the design, conduct or reporting of research in institutions under the oversight of NHG DSRB are required to complete the FCOI training requirements. This is also applicable to study team members who are from external institutions, i.e. not directly employed by NHG or its partner institutions.

The FCOI training course is a sub-component of the CITI programme, and comprises the following two core modules:

1. NHG-Singapore. Overview of Domain Specific Review Board (DSRB) Review Process (ID: 810)\*;
2. Conflicts of Interest in Human Subjects Research (ID: 17464 or 488)\*  
*(Please refer to footnote under table 10 above.)*

*\*Course code is subjected to change. Please refer to the NHG Research Website for the most updated course code.*

Investigators (and study team members) who have obtained their CITI certification would have, by default, completed the FCOI training requirements, as the 2 modules for FCOI training are encompassed within the 10 core modules in the CITI programme.

For investigators and study team members who have not obtained / are not required to obtain CITI certification:

- Where CITI is a minimum training requirement (i.e. for PIs conducting clinical research studies, or co-investigators), investigators will have to complete the CITI course as stipulated above. Completion of CITI will automatically ensure that the FCOI training requirements are met, as the FCOI-related training modules are encompassed within the CITI course requirements.
- Where CITI is not a minimum training requirement (i.e. for PIs conducting clinical trials, or other study team members), investigators and study team members will only be required to complete the 2 FCOI-related training modules listed above. It is not mandatory to complete the full set of 10 core modules and 5 elective modules in CITI.

For more information, please refer to <https://www.research.nhg.com.sg> > Conducting Research > Who can be a Principal Investigator > Minimum Training Requirements > Financial Conflict of Interest (FCOI) Training Requirements for All Investigators and Study Members.

### **IV. RI Specific Minimum Training Requirements**

There may be specific minimum training requirements set by individual Research Institutions (RIs).

From 1 November 2019, **all NHG Institution staff (PIs, Site-PIs, Co-Investigators and study team members)** involved in the design, conduct or reporting of new HBR studies / sites\* approved by a NHG appointed IRB (i.e. DSRB, SingHealth CIRB, NUS IRB, NTU IRB), will be required to complete the NHG HBR Essential Conduct of Research (ERC) Course as part of the minimum training requirements prior to the commencement of their study involvement.

\* sites: refers to any new sites added to any ongoing HBR research protocol.

The NHG HBR ERC Course is also applicable to all:

**NHG-based MOHH residents/doctors** who are participating in HBR studies (approved by NHG appointed IRB from 1 November 2019) in the capacity of NHG PI / Co-I or Study Team, **from 1 October 2020**.

**NHG-based SAF staff/doctors\*** who are participating in HBR studies (approved by NHG appointed IRB from 1 December 2021) in the capacity of NHG PI/Co-I or study team member, **from 1 December 2021**.

*\*Staff with formal appointment with NHG Institutions (including affiliate or joint appointments).*

Researchers and study team may be exempted from or apply for a waiver to complete the NHG HBRA minimum training requirements.

For more information, please refer to <https://www.research.nhg.com.sg> > Conducting Research > Minimum Training Requirements > HBR Essential Research Conduct (ERC) Course.

**For non-NHG Institutions:** Researchers are advised to check with their RI to complete the specific additional RI minimum training requirements.

### 3.2.2 Minimum Training Requirements for Staff from NHG and Partner Institutions

The minimum training requirements for staff from NHG and partner institutions are based on their roles in the research study. Table 11 below summarises the DSRB minimum training requirements.

Table 11: DSRB minimum training requirements

Study Role	GCP	NHG CITI	NHG CITI FCOI *
PIs and Site PIs conducting clinical trials	Yes (regardless of whether CITI has been completed)	No	Yes
PIs and site PIs conducting research studies other than clinical trials	No	Yes	Yes
Co-investigators	No	Yes	Yes
Other study team members	No	No	Yes

\* All study team members who are involved in the design, conduct or reporting of research in institutions under the oversight of the NHG DSRB are required to complete the NHG FCOI training requirements.

### **3.2.3 Minimum Training Requirements for Staff from SingHealth and Partner Institutions**

The SingHealth CIRB minimum training requirements are slightly different from that of DSRB. The CIRB requirements will apply to staff from SingHealth and its partner institutions who are involved in cross-cluster studies that are submitted to DSRB for review. Table 12 below summarises the CIRB minimum training requirements.

*Table 12: CIRB minimum training requirements*

<b>Study Role</b>	<b>ICH GCP</b>	<b>SingHealth CITI</b>	<b>NHG FCOI^</b>
PIs and Site PIs conducting clinical trials	Yes	Yes	No
PIs and site PIs conducting research studies other than clinical trials	No	Yes	No
Co-investigators	No	Yes	No^
Other study team members	No	Yes	No^

<sup>^</sup> If a staff from SingHealth or its partner institutions is involved in the design, conduct or reporting of a research that is conducted in NHG or its partner institutions, the minimum training requirements for NHG FCOI training requirements will apply to him / her.

### **3.2.4 Minimum Training Requirements for Staff from Other External Institutions**

Study team members who are from other external institutions (i.e. not from NHG / SingHealth or its partner institutions) should refer to their institution guidelines on CITI, GCP training or other applicable minimum training requirements.

### **3.2.5 Waiver of Minimum Training Requirements**

#### **Waiver to complete the CITI or GCP courses**

If an investigator has attended any other course relevant to research ethics, he / she may apply for a waiver of the requirements to complete the CITI or GCP courses. This request will be reviewed by the DSRB and the waiver granted on a case-by-case basis.

#### **I. Criteria to Qualify for a Waiver of CITI Certification**

DSRB accepts the ICH GCP certificate as completion of the minimum training requirements. However, if you have completed other research ethics training programmes that are organised and conducted by a reputable body such as NHG institutions, Health Sciences Authority, National University of Singapore etc., you may apply for a waiver of the CITI Program for DSRB's evaluation. Any program that qualifies as a research ethics training equivalent of CITI should be at minimum, an 8-hour programme and should address the following topics:

- a. History and ethics principles of research ethics
- b. Regulatory framework and guidelines in Singapore
- c. Informed consent
- d. Privacy and confidentiality Issues

The GCP training course from the National University Health System cannot be used to waive the completion of the CITI Program.

It should be noted that approval granted for a waiver of CITI certification does not exempt investigators from the FCOI training requirements.

*For more information, please refer to <https://www.research.nhg.com.sg> > Conducting Research > Minimum Training Requirements > Collaborative Institutional Training Initiative (CITI).*

## **II. Criteria to Qualify for a Waiver of GCP Certification**

Experienced investigators who have assumed the roles and responsibilities of a PI for multiple clinical trials may apply for a waiver of the additional requirement provided the following conditions are met:

- a. The applicant must have conducted a minimum of five (5) clinical trials, either as a PI or site PI, within NHG or its partner institutions under the oversight of DSRB over the last six (6) years;
- b. The applicant must have enrolled at least one subject for these clinical trials (stated in a); and
- c. The applicant certifies that there were no major research ethics violations, non-compliances, unjustified DSRB SOP deviations, research misconduct and / or complaints for these clinical trials (completed and ongoing).

The supporting documents for the waiver of GCP course completion will be reviewed and approved by the REC Chairperson or any other members appointed by the REC Chairperson to do so.

It should be noted that approval granted for a waiver of GCP certification does not exempt investigators from the FCOI training requirements.

*For more information, please refer to <https://www.research.nhg.com.sg> > Conducting Research > Minimum Training Requirements > Good Clinical Practice (GCP) Training For Principal Investigators of Clinical Trials.*

### **3.3 Responsibilities of a PI**

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The PI is the person primarily responsible for the proper conduct of the research study. If a team of individuals is involved in the conduct of the research study, the PI is responsible for the oversight of the research team.

The PI bears the overall responsibility for completing and submitting the DSRB Application Form on ROAM, even if these tasks have been delegated to other research staff. The rights, safety and well-being of the research subjects are of utmost importance, and the research proposal should demonstrate that there are adequate provisions to protect rights, safety and well-being of research subjects.

The PI must adhere to the following declarations:

- a. Ensure written approval/ notification/ acknowledgement is obtained from the IRB and relevant authorities (e.g. Ministry of Health (MOH), Health Sciences Authority (HSA), where applicable) prior to the start of the study or when instituting any changes to the protocol.
- b. The PI will not initiate any change in protocol without prior written approval from the DSRB except when it is necessary to reduce or eliminate immediate risk to the subjects. Thereafter, the PI will submit the proposed amendment to the DSRB and other relevant authority(ies) for approval.
- c. The PI will promptly report any unexpected or serious adverse events, unanticipated problems or incidents that occur in the course of the study, in accordance with applicable safety reporting guidelines.
- d. The PI will maintain all essential documents and recognise that the DSRB and / or other regulatory authorities may inspect these records.
- e. The PI understands that failure to comply with all applicable regulations, institutional and DSRB policies and requirements may result in the suspension or termination of this study.
- f. The PI declares that there are no conflicting interests for any of the research personnel participating in the study, as well as their immediate family members. Should there be any conflicts of interest, the PI must declare these in the ROAM online application form and describe the plan to remove or manage the conflict of interest.

Co-investigators are members of the research team designated and supervised by the PI at a site to perform critical study-related procedures and / or make important research-related decisions (e.g. associates, residents, research fellows).

Collaborators are members of the research team designated by the PI to assist with research-related activities that do not involve subjects contact (e.g. scientist, research fellow, data analyst, etc.).

Research assistant / clinical research coordinators / research nurses are members of the research team designated by the PI to handle the administrative and /or clinical responsibilities

of a research study. Synonyms include trial coordinator, research coordinator, clinical coordinator, and clinical trial coordinator.

### **3.3.1 Qualifications and Agreements**

The PI must be qualified by education, training and experience to assume the responsibilities associated with proper conduct of a research study, and should meet all qualifications specified by the applicable regulatory requirements.

For the conduct of clinical trials, a qualified practitioner under the Health Products (Clinical Trials) and Medicines (Clinical Trials) Regulations refers to an individual who is:

- a. A registered medical practitioner under the Medical Registration Act (Cap. 174); or
- b. A registered dentist under the Dental Registration Act (Cap. 76) whose name appears in the first division of the Register of Dentists maintained and kept under section 13(1)(a) of that Act.

The PI should be thoroughly familiar with the study protocol. When conducting clinical trials, the PI should be thoroughly familiar with the investigational product(s) as described in the investigator's brochure, product labelling and / or other sources. The PI should maintain a list of appropriately qualified persons to whom he / she has delegated significant research-related responsibilities (e.g. study responsibility / delegation log).

### **3.3.2 Adequate Resources**

The PI should have sufficient time and adequate qualified personnel (including co-investigators, collaborators, and other research staff) to properly conduct and complete the research.

The PI should ensure that all persons assisting with the research are adequately informed about the protocol, the investigational product(s) and their research-related duties.

### **3.3.3 Medical Care of Subjects**

Any qualified practitioner who is the PI or a co-investigator of the research study, who is registered with the appropriate professional board, is responsible for all research related medical (or dental) decisions.

The PI should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the research.

### **3.3.4 Communication with DSRB**

The PI should obtain written approval from the DSRB before initiating a research project involving human subjects, when the research is conducted by or under the direction of any employee of NHG, or the research is conducted using the facilities of any institutions which conduct research under the oversight of NHG DSRB.

The PI should ensure all relevant reports are submitted per DSRB's requirements. These reports may include study amendments, study status reports, safety events and non-compliance reporting.

*Please refer to chapter 4 Submissions to DSRB for a detailed description of the documents that must be submitted to the DSRB before the initiation of a research study, during the course of the research study, as well as after completion of the research study respectively.*

### **3.3.5 Compliance with the Protocol**

The PI should conduct research in compliance with the approved protocol and all applicable research SOPs, policies and regulations.

The PI should not implement any deviation from or changes to the protocol without agreement by the sponsor and prior review and documented approval from the DSRB and relevant regulatory authorities (where applicable), except where necessary to eliminate an immediate hazard(s) to subjects.

The PI bears direct responsibility for the conduct of the research study. The PI should employ sound study design in accordance with standards of the discipline. The study design should minimize risks and maximise benefits. In studies involving greater than minimal risks to subjects, the PI must submit a data safety monitoring plan for review and approval by the DSRB and relevant regulatory authorities (where applicable), and comply with the plan.

### **3.3.6 Informed Consent of Research Subjects**

The PI and / or research staff must recruit subjects in a fair and equitable manner, weighing the potential benefits of the research to the subjects against their vulnerability and risks involved.

The PI must ensure that informed consent is obtained from subjects prior to their enrolment into the research, unless this requirement is waived by the DSRB. The PI must use the latest approved version of the consent documents approved by the DSRB.

*Please refer to chapter 5 Informed Consent for more details on the informed consent process for research studies.*

### **3.3.7 Safety Reporting**

The PI must report all UPIRTSOs that occur during the conduct of a research project to the DSRB, in accordance with the timelines set by DSRB. For HBRA-regulated studies, Expected SAE(s) should also be reported to DSRB.

*For more information on UPIRTSOs, please refer to chapter 4.7 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs) and Expected Serious Adverse Events (SAE).*

SAEs / USADRs should be reported to the RI, sponsor and/or regulatory authorities where applicable, in accordance with safety reporting guidelines and within the stipulated timelines.

### **3.3.8 Other Obligatory Reporting Requirements**

The PI must report to relevant authorities if any research subject is suspected of having a notifiable disease according to relevant regulations and institutional requirements.

If abuse or neglect of a child or an elderly person is detected, the PI must ensure that this is reported to relevant authorities and in accordance to institutional requirements.

### **3.3.9 Records and Reports**

The PI must maintain all essential documents for the research study in an investigator file, and recognise that the DSRB and / or applicable regulatory authorities may inspect these documents.

*For a list of the essential documents to be maintained for the conduct of a clinical trial, please refer to sections 8.2, 8.3 and 8.4 of the ICH GCP E6 (R2).*

*The Investigator File Contents Template is available at <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOP & Templates.*

The PI must ensure the accuracy and completeness of data in all study databases and reports.

#### **Duration of Record-Keeping**

For clinical trials regulated by HSA, the essential documents should be retained at least until the later or the latest, as the case may be, of the following:

- a. the date where there is no more pending or contemplated application for registration under the Health Products Act of the therapeutic product/for a product licence for the medicinal product being tested in the clinical trial;
- b. the expiry of 2 years after the last of such registrations is granted/after the last approval of such application for the medicinal product to be tested in Singapore;

- c. where the clinical trial is terminated, the expiry of 2 years after HSA has been informed of the termination of the trial under regulation 12 of the Health Products or Medicines (Clinical Trials) Regulations 2016;
- d. the expiry of 6 years after the conclusion of the clinical trial;
- e. the expiry of such other period as HSA may direct in any particular case.

Nonetheless, essential documents should be retained for a longer period, if required by the applicable regulatory requirements, or by an agreement with the sponsor.

For all other research studies, NHG institutional policies require that the essential documents be retained for at least 6 years after completion of the research study. For studies conducted in non-NHG institutions, the PI should check the institutional requirements for the minimum archival period.

*For more information on record-keeping for essential documents, please refer to:*

- *NHG PCR SOP 501-B05 Documentation;*
- *Chapter 2.2 The Regulation of Clinical Trials and Clinical Research Materials.*

### **3.3.10 Clinical Research Materials (CRM)**

The PI is responsible for the accountability of all CRM used at the study site. The PI may assign some or all duties related to CRM accountability at the study site to a study pharmacist or another appropriately trained individual.

In accordance with the prescribed regulatory requirements, the PI should maintain appropriate accountability logs to accurately document the receipt, storage, use and destruction of the CRM. The PI should also ensure that the CRM are stored and dispensed in compliance with the approved protocol.

*For more information on the regulatory requirements for CRM, please refer to:*

- *NHG PCR SOP 501-B05 Documentation*
- *Chapter 2.2 The Regulation of Clinical Trials and Clinical Research Materials.*

*Study templates for CRM inventory, dispensing and accounting logs are available at <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOP & Templates.*

### **3.3.11 Randomisation Procedures and Unblinding**

The PI should follow the study randomisation procedures (if any) and ensure that the randomisation code is broken only in accordance with the protocol. If the study is blinded, the PI should promptly document and explain to the sponsor (if applicable) any instances of premature unblinding (e.g. accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

### **3.3.12 Premature Termination or Suspension of a Trial**

The PI should promptly inform the trial subjects and ensure appropriate therapy and follow-up for the subject if the study is prematurely terminated or suspended for any reason.

The PI should inform DSRB and the relevant regulatory authorities if the study is prematurely terminated or suspended for any reason.

### **3.3.13 Conflict of Interest**

The PI and each member of the research team must declare on the application form to the DSRB whether the study team members or their immediate family members have any financial conflicts of interest related to the research study. The declaration should give full disclosure of the facts giving rise to the financial interest, and detail the proposed steps to eliminate any conflicts of interest that arise from the financial interest.

Conflicting interests may also arise during the conduct of the study. If such interests arise, the PI and each member of the research team should declare these to DSRB.

*For more information on declaring and managing financial conflicts of interest, please refer to chapter 3.5 Financial Conflict of Interest (FCOI).*

### **3.3.14 Sponsored Clinical Trials**

The PI and the sponsor must sign a Clinical Trial Agreement. The PI should ensure that the clinical trial is conducted according to the signed agreement.

## **3.4 Change of PI and / or Study Team Members**

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### **3.4.1 Change of PI**

If the PI is resigning from his / her institution or is going away for an extended duration of time, the oversight of the research study should be formally delegated to another investigator (e.g. a co-investigator). This investigator should fulfill all qualifications for being a PI as per DSRB requirements. The incoming investigator will assume all the responsibilities as the PI for the conduct of the research study, until the original PI returns.

- i. For more than minimal risk studies, the study should be formally transferred to another investigator if the PI will be away for more than 3 months.
- ii. For less than minimal risk studies, where subject recruitment and follow-up activities are still ongoing, the study should be formally transferred to another PI, if the original PI will be away for more than 6 months.

Any change in the PI should be documented in study responsibility log. This change in the PI should also be reviewed and approved by the DSRB.

The existing PI must submit a study amendment cover note, along with the relevant documents, to the DSRB for approval. For a change in PI, the relevant documents should include (but is not limited to) the prospective investigator's latest CV (updated within the past one year).

Approval for a change of PI should also be obtained from relevant regulatory authorities as per regulatory requirements.

### **3.4.2 Changes in Study Team Members**

DSRB must be kept informed of any change(s) to the following study team members:

- PI (as described above)
- Co-investigator(s)
- Collaborator(s)

Any addition(s) or removal(s) of the abovementioned study team members to / from the study team member list must be submitted to the DSRB via a study amendment application. The existing PI must submit a study amendment cover note, along with any relevant documents, to the DSRB for review. DSRB approval must be received before the changes to the study team members may be implemented.

If other institutional staff (e.g. research manager, study coordinator) who are not PI, Co-I(s) and Collaborator(s) wishes to have access to the DSRB application form, the PI should include them as Study Administrators in the DSRB application form. Study Administrators should also be removed if they no longer require access to the application form. DSRB would acknowledge the additional or removal of Study Administrators in the application form.

Change(s) to the study team member list involving other study roles not mentioned above (e.g. research coordinator, pharmacist, laboratory technician, etc.) do not need to be submitted to the DSRB for review. However, the PI must update the study responsibility log with these study team member changes in a timely manner. Any FCOI declaration requirements to DSRB for new study team members will also apply (see subsequent section on FCOI).

## **3.5 Financial Conflict of Interest (FCOI)**

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Conflicting interest – A conflicting interest can be broadly defined to refer to any interest of the investigator and / or any study team member that competes with the investigator's and/or study team member's obligation to protect the rights and welfare of research subjects.

Financial interest – Significant financial interest means anything of monetary value, including but not limited to, salary or payments for services (e.g. consulting fees or honoraria); equity

interests (e.g. stocks, stock options or other ownership interests); intellectual property rights (e.g. patents, copyrights and royalties from such rights), and board or executive relationships.

Investigators and study team members should not have conflicting interests that may adversely affect the protection of subjects or the credibility of the human subject protection programme.

### **3.5.1 Identifying FCOI**

The PI must reveal to DSRB if any of the investigators, study team members or their immediate family members have any financial interest related to the research study as follows:

- a. Financial interests (e.g. stocks, stock options or other ownership interests) in the assets or liabilities of any company that may benefit from the research activity.
- b. Payments (e.g. salary, consultation fees, speaking fees, or honoraria) from any company that may benefit from the research activity.
- c. Employment or executive relationships with any company that may benefit from the research activity.
- d. Intellectual property rights or proprietary interests (e.g. patents, copyrights and royalties from such rights) related to the research.
- e. Options or other compensation arrangements that could be affected by the outcome of the research.

### **3.5.2 Disclosure of Financial Interests to DSRB**

The PI must reveal on the initial application to the DSRB, annually and at any point arising during the conduct of the study if any of the investigators, study team members or their immediate family members have any financial interests related to the research study as follows:

- a. Any compensation by any commercial sponsor company of the study in which the value of compensation could be affected by study outcome.
- b. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.
- c. Any equity interest in any commercial sponsor of the study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the investigator or study team member is carrying out the study and for one year following completion of the study.

- d. Any equity interest in any commercial sponsor of the covered study if the commercial sponsor is a publicly held company and the interest exceed \$10,000 in value or 10% of the voting stock or controlling interest of the commercial company (whichever is lower). The requirement applies to interests held during the time the investigator or study team member is carrying out the study and for one year following completion of the study.
- e. Significant payments of other sorts (SPOOS) that have a cumulative monetary value of \$10,000 and are made by any commercial sponsor of the study to the investigator, study team member or their institution during the time the investigator or study team member is carrying out the study and for one year following completion of the study. This would include payments that support activities of the investigator or study team member (e.g. a grant to the investigator or to the institution to specifically fund the investigator's other ongoing research or compensation in the form of equipment that is not meant to be used for the study), or to provide other reimbursements such as retainers for ongoing consultation or honoraria. Payments for the cost of conducting the study or other studies which are already under a contractual arrangement with the commercial sponsor(s), as well as miscellaneous payments that would be controlled by the institution's finance/HR department (e.g. transportation and accommodation costs to attend investigators' meetings) are excluded.

Researchers and research staff members who are reviewing and endorsing study applications in the role of a DR or IR must reveal to the DSRB if they or their immediate family members have any financial interests related to the research being endorsed.

The declaration should give full disclosure of the facts giving rise to the financial interest and to detail the steps proposed to eliminate any conflict of interest that arises from the financial interest.

### **3.5.3 Timelines for FCOI Declarations to DSRB**

#### **I. At initial Application to DSRB**

The Principal Investigator must reveal on the initial application to the DSRB if any of the investigators, study team members or their immediate family members have any financial interests related to the research study.

Refer to section 3.5.2 Disclosure of Financial Interests to DSRB for more details.

#### **II. Annual FCOI Declaration**

The FCOI declaration cycle is an annual process, and will be held from 01 December (of the current year) to 31 January (of the next year). The validity will be from the date the FCOI declaration form is submitted during the cycle, till 31 December. Principal investigator(s) and all study team members involved in the design, conduct or reporting of research will each need to complete and submit their individual FCOI form for their declaration of their financial status. The completed form is to be submitted to the DSRB FCOI secretariat ([DSRB\\_FCOI@nhg.com.sg](mailto:DSRB_FCOI@nhg.com.sg)).

If any study team member had missed the period for the annual FCOI declaration cycle, he / she can still submit the declaration form at any time throughout the year. However, the declaration will only be valid until the next declaration cycle. For example, if the declaration form was submitted in 1 August 2021, this declaration would be valid only from 1 August 2021 till 31 December 2021.

### **III. FCOI Arising During Conduct of the Study**

FCOI may also arise during the conduct of the study. If such interests arise, the investigator and / or affected study team member(s) should submit an updated FCOI declaration form as soon as possible, but not later than 30 calendar days following first knowledge of these conflicting interests. The updated FCOI declaration form should be submitted to the DSRB FCOI secretariat ([DSRB\\_FCOI@nhg.com.sg](mailto:DSRB_FCOI@nhg.com.sg)).

Researchers and research staff members who are reviewing and endorsing study applications in the role of a DR or IR must also reveal to the DSRB if they or their immediate family members have any financial interests related to the research being endorsed. The DRs and IRs will be prompted to make the declaration every time they review a study that is due for submission to the DSRB. If the DR and / or IR has a conflict of interest, he / she will need to inform the DSRB and the study will be routed to another DR / IR who does not have a conflict of interest, for endorsement.

### **IV. Other Notable Time points for Submitting FCOI Declarations**

*Table 13: When to submit and what to submit for FCOI declarations*

<b>Submission Time Point</b>	<b>What To Do</b>	<b>Where To Submit</b>
At initial DSRB application	The PI will need to submit a separate Study Team Member List for FCOI Declaration [Form ID: 205-034] if there are team members NOT listed in Section B1(iii) of the Biomedical Study Application Form/Section B2 of the Population Health Study Application Form (e.g. research nurses, research coordinators, etc.) and are involved in the design, conduct or reporting of research conducted under the oversight of NHG or its partner institutions.	The Study Team Member List for FCOI Declaration [Form ID: 205-034] is to be attached in the initial DSRB Application Form.
At continuing review	The Study Team Member List for FCOI Declaration [Form ID: 205-034] is to be attached along with the Study Status Report for submission to DSRB.	

For new study team members (i.e. those who have newly joined the study team while the research is ongoing, and who are not listed in Section B1(iii) of the Biomedical Study Application Form/Section B2 of the Population Health Study Application Form (e.g. research nurses, research coordinators, etc.) and are involved in the design, conduct or reporting of research conducted under the oversight of NHG or its partner institutions; the PI will need to ensure that the new study team member:

- Completes the applicable FCOI training requirements, where applicable (please refer to chapter 3.2 for details);
- Submits a completed FCOI declaration form to the DSRB FCOI Secretariat; and
- Is added into the Study Team Member List submitted to DSRB during the annual continuing review.

### **3.5.4 Review and Management of FCOI**

The DSRB will review the disclosed financial interests to determine their impact on the integrity of the research and whether the management plan to eliminate any conflict of interest is appropriate. The DSRB may impose a management plan to eliminate, mitigate or manage the financial interests. Possible measures that may be taken to resolve the financial conflicts of interest may include (but are not limited to):

- a. Disclosure of the conflict in the consent document;
- b. Modification of research plan;
- c. Divestiture of financial interest;
- d. Severance of the relationship that created the conflict;
- e. Training on conflicts of interest for all personnel involved in the research;
- f. Disqualification from participation in all or a portion of the research; and/or
- g. Audit of research by independent reviewers or review committees.

Investigators who are also the inventors of the investigational product/device should not be prohibited from participating in the research as they would be most familiar with the investigational product/device. It should first be considered if additional mitigation measures could be put in place to mitigate the financial conflict. These measures may include, but is not limited to:

- a) Increased monitoring or audit frequency by the Research Institution(s)/independent reviewer(s)/review committee(s);
- b) Preventing the investigator(s) from receiving any Intellectual Property-related payouts during the interim period before there is sufficient evidence-based recommended usage of the investigational product/device;
- c) Restricting the investigator(s)'s involvement in the research (e.g. he/she should not participate in the safety and efficacy assessments, data analysis, and/or report writing); and/or

- d) Allowing the investigator(s)'s to conduct only the initial proof-of-concept study on a limited number of subjects (e.g. no more than 20 subjects in the study).

The PI will be informed by the DSRB if any modifications are required to the management plan to eliminate or mitigate the identified conflicts of interest.

*For more information, please refer to <https://www.research.nhg.com.sg> > Conducting Research > Minimum Training Requirements > Financial Conflict of Interest (FCOI) Training Requirements for All Investigators and Study Members.*

### **3.6 Institutional Conflict of Interest (ICOI)**

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ICOI in human subject research is defined as a situation in which the relevant financial investments or holdings of NHG, its partner institutions or the personal financial interests or holdings of institutional officials might affect or reasonably appear to affect institutional processes for the design, conduct, reporting, review, or oversight of human subject research.

To manage ICOI, each institution administers its own ICOI policies and framework, including the appointment of an ICOI Review Committee to evaluate ICOI declarations.

Under NHG's ICOI policy, a financial interest is deemed significant when it exceeds the applicable threshold for each specific category of financial interest, as established and periodically disseminated by the REC or designated ICOI Review Committee / designee.

With effect from 01 January 2015, the institution and Institutional Officials shall declare the financial interests annually via a Declaration Form. The declaration shall also include the financial interests of their immediate family members (includes spouse and dependent children) if known. The institution and Institutional Officials will be reminded at the 6-month interval to submit an updated declaration if there is a change in the circumstance that alters the previous declaration.

Once a potential ICOI has been identified by the ICOI secretariat, the ICOI Review Committee will be informed to evaluate the ICOI. The ICOI Review Committee's decision and report will be provided to the DSRB so that the ethics review of the research project can consider the deliberations and recommended management of the ICOI. The DSRB has the final authority to ensure if the conflict of interest management plan is adequate and whether the research can be approved. The DSRB will engage the ICOI Review Committee to consider all possible management plans before deciding to terminate any research.

# **CHAPTER 4**

# **SUBMISSIONS TO DSRB**

## **4.1 The Application Process**

## **4.2 Submission of New Applications**

## **4.3 Review of Submitted Applications**

## **4.4 Outcome of Review**

## **4.5 Study Amendments**

## **4.6 Continuing Review**

## **4.7 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) and Expected Serious Adverse Events (SAE)**

## **4.8 Non-Compliances / Study Deviations**

## **4.9 Changes in Study Status**

## **4.10 Other Notifications**

## **4.1 The Application Process**

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### **4.1.1 Research Online Administration and Management (ROAM) System**

Research applications must be submitted to the DSRB for review via ROAM. The ROAM portal may be accessed via the NHG Research website at <https://www.research.nhg.com.sg>.

*To help researchers navigate the ROAM system, ROAM guidebooks are available at <https://www.research.nhg.com.sg> > Resources > ROAM Guidebooks.*

### **4.1.2 Timeline for Submission of Applications**

The submission deadline for new research studies requiring Full Board review and major amendments is the 15<sup>th</sup> day of every month, or the next earliest working day if that day falls on a weekend or a public holiday.

The only exception is Biomedical Domain B1, where the submission deadline for Full Board studies is the 1<sup>st</sup> working day of the month, or the next earliest working day if that day falls on a weekend or public holiday.

The PI should submit applications with sufficient lead time for the DR and IR to endorse, prior to the submission deadline for the month (please see section 4.1.3 below). Submissions meeting the stipulated deadlines will be tabled for the next Full Board meeting (subject to completeness of the submission and Full Board agenda items).

Research studies of less than minimal risk that qualify for Expedited review, applications with a request for exemption status, and minor amendments to DSRB-approved research studies may be submitted at any time of the month. These studies will be reviewed by the domain chairperson on a weekly basis.

*For more information on the DSRB meeting dates for the year, please refer to <https://www.research.nhg.com.sg> > Ethics & Quality > Apply for Ethics Approval > Ethics Review Meeting Dates > Determine if Ethics Review is required & Meeting Dates*

*For more information on the different categories of review for new applications, please refer to section 4.3.1.*

*For more information on the different categories of review for study amendment applications, please refer to section 4.5.2.*

### **4.1.3 Endorsement by the Institution**

Prior to making a submission to DSRB, investigators are required to obtain endorsements from their DR and IR.

- Once the PI submits an application, it will be automatically routed to the DR for endorsement.
- After the DR has endorsed the application, it will be automatically routed to the IR for endorsement.
- DSRB will receive the application only after both the DR and IR have endorsed it.

As mentioned in section 4.1.2 above, PIs should allocate sufficient time for their DR and IR to endorse their study application(s), prior to the application(s) reaching DSRB before the submission deadline for the month.

*For more information on the roles of the DR and IR, please refer to chapter 1.3 Role of Institutions, Department and Institution Representatives, Investigators and Other Study Team Members.*

#### **4.1.4 Triaging of Studies to the Relevant DSRB Domain**

All research studies submitted to the DSRB will undergo an appropriate in-depth review.

The PI should select the most appropriate DSRB domain to review their study in section B3 of the ROAM application form. The research application will first be assigned to the domain selected by the PI, but may be assigned to another domain based on DSRB secretariat's determination.

The DSRB will evaluate the PI's choice of domain based on the following considerations:

- PI'S discipline – A research study will be triaged to the domain that reviews the discipline under which the study may be categorised.
- Disease studied in the research study – Depending on the primary disease group that is being studied in the research study, the study will be triaged to the domain that includes experts in this disease group.

Where there is uncertainty about which domain a study should be triaged to, the decision will be escalated to the Triage Board. The Triage Board is a virtual board consisting of the DSRB chairpersons or their deputies.

#### **4.1.5 Mutual Recognition of Research Review Between SingHealth CIRB and NHG DSRB**

Since 22 May 2014, the two public healthcare clusters SingHealth and NHG have established an arrangement for mutual recognition of IRB review and approvals. All new research applications involving both SingHealth and NHG sites are eligible to benefit from the CIRB-DSRB mutual recognition arrangement and have their studies reviewed by only one IRB.

From 1<sup>st</sup> October 2014, cross-cluster research applications can be submitted to either SingHealth CIRB or NHG DSRB, depending on the Overall PI's cluster.

*For more information on cross-cluster research applications, please refer to <https://www.research.nhg.com.sg> > Ethics & Quality > [DSRB Announcements](#) for the Updated FAQs on the Mutual Recognition of Research Ethics Review between SingHealth-CIRB and NHG DSRB.*

#### **4.1.6 Collaborative Agreement Between Other IRBs and NHG DSRB**

For collaborative research studies between NHG institutions and NTU/NUS researchers, NHG DSRB has established Cooperative Agreements with NTU IRB and NUS IRB, to determine the type of studies to be reviewed by the respective IRBs.

*For more information on the collaborative research applications, please refer to <https://www.research.nhg.com.sg> > Ethics & Quality > Research Ethics Framework > DSRB Frequently Asked Questions (FAQs) > General FAQs*

## **4.2 Submission of New Applications**

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PIs are strongly encouraged to submit their application well before the stipulated submission deadline, to allow time for the DSRB to check for any missing documents and / or information.

The materials submitted must provide the DSRB with sufficient information about the research study, in order for the DSRB to adequately assess if the application meets the criteria for approval. A submitted research proposal will be scheduled for DSRB review only when the DSRB secretariat has determined that the information and materials submitted provide an adequate description of the proposed research.

### **4.2.1 Supporting Documents Required for New Applications**

A new application must include (but is not limited to) the following supporting documents:

- a. A completed ROAM online DSRB application form;
- b. ICF / application for waiver of informed consent;
- c. Study protocol (this is mandatory for clinical trials involving drugs, medical devices and surgical procedures);
- d. Questionnaires, surveys, videotapes and other such research tools (if used);
- e. Copy of the approved grant application or notification of award (if the study is a US federally funded research, the approved grant application, study protocol and sample consent form, etc.);

- f. Investigator's Brochure and other available safety information (for all HSA regulated clinical trials);
- g. Recruitment materials intended to be seen or heard by potential subjects, including email solicitations and physician letters (if used);
- h. Written information intended to be provided to subjects (if used);
- i. Incidental Findings Management Plan;
- j. Curriculum vitae (CV) of PIs and co-investigators, updated within the past one year;

In addition, applicants may be requested to submit:

- a. Data Collection Form;
- b. Financial disclosure statement;
- c. Clinical trial agreement (for industry-sponsored research);
- d. Documentation relating to non-approval of study by another IRB;
- e. Any other relevant documentation to be given to subjects when, in the judgment of the DSRB, the additional information would add meaningfully to the protection of the rights, safety and / or wellbeing of the subjects,
- f. Any other relevant documentation that the DSRB may specifically request.

With effect from 1 June 2020, translated Informed Consent Forms (fully translated or short consent forms) will not need to be submitted to DSRB for acknowledgment / approval.

With effect from 19 Oct 2020, all translated documents (such as posters, flyers, brochures, patient diaries/cards, questionnaires, assessments, etc.) will not need to be submitted to DSRB for acknowledgement.

However, the PI should ensure the accuracy of the translations and ensure that correct versions of the translated documents are used. All versions of the translated documents to be used should be tracked in the investigator file.

#### **4.2.2 Materials for Subject Recruitment**

Any materials to be used to publicize the intention to recruit research subjects should be used only after approval by the DSRB. Recruitment strategies include direct advertising, dear doctor letters, etc. This information should be provided in the ROAM application form.

Payment of finder's fees and / or recruitment bonuses for subject recruitment is not permitted. The DSRB will not approve such the use of such payments in the subject recruitment process.

- Finders' fees are defined as payments from the investigator or sponsor to a person who refers a potential subject.
- Recruitment bonuses are defined as payments from the sponsor to an investigator or organisation based on the rate or timing of recruitment.

The DSRB has no objection to the use of direct advertising to find potential research subjects. Direct advertising includes, but is not limited to:

- a. Newspaper advertisements;
- b. Posters, bulletins, flyers, brochures;
- c. Email messages;
- d. Invitation letters to potential subjects.

DSRB's review and approval is not required in the following cases:

- a. Letters to doctors for referring potential subjects;
- b. Stories in newspapers or magazines that mention the research project;
- c. Listing of clinical trials on internet websites, when the format is limited to basic trial information such as protocol title, purpose of study, protocol summary, basic eligibility criteria, study site location and how to contact the site for further information.

## **I. Preparing Advertisements for Subject Recruitment**

Submissions for review of advertisements by the DSRB should include information on:

- a. Where the material will be used e.g. newspaper, radio including number of times the advertisement will be run;
- b. Locations of posters / flyers,
- c. Final copy of the advertisement for printed material, and / or video or audio tape that will be used for the broadcast.

Advertisements to recruit subjects should be limited to information that prospective subjects need to determine their eligibility and interest. The following information must be included:

- a. That volunteers are being recruited for research;
- b. The name and address of the institution conducting the research;

- c. The condition under study and / or the purpose of the research;
- d. In summary form, the criteria that will be used to determine eligibility for the study;
- e. A brief list of participation benefits, if any (e.g. no-cost health examination);
- f. The time or other commitment required of the subjects;
- g. The location of the research and the person or office to contact for further information.

The advertisement should not, either explicitly or implicitly:

- a. State or imply a certainty of favourable outcome or other benefits beyond what is outlined in the ICF and protocol;
- b. Make claims that the drug, device or biologic is safe or effective for the purposes under investigation;
- c. Make claims that the test article is known to be equivalent or superior to any other drug, biologic or device;
- d. Use terms such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational;
- e. Promise “free medical treatment,” when the intent is only to say participants will not be charged for taking part in the investigation. Advertisements may state that participants will be paid, but should not emphasise the payment by such means as larger or bold type. Advertisements should not state the amount that will be paid;
- f. Include any exculpatory language;
- g. Make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with currently approved labelling.

## **II. Payment to Research Subjects**

The ICF should include information on payment arrangements for participants who participate in the research. The DSRB will consider the following issues while reviewing the payment arrangements:

- a. Payment to the participants for participation is not considered a benefit, but a reimbursement for the participants’ time and expenses incurred.
- b. The amount and proposed method and timing of payment should not present any undue influence.

- c. Payment to participants should be pro-rated, and not be contingent upon the participants completing the study.
- d. Payment of a small proportion as an incentive for completion is acceptable, providing the incentive is not coercive.
- e. Compensation for participation should not include coupons for discount on the price of the study material after the product is approved for marketing.

Investigators may refer to table 14 for guidelines on payments to research participants:

Table 14: Guidelines for research subject payments

<b>Study Visit Required by Subject</b>	<b>Payment Serves As</b>	<b>Amount Paid to Participant</b>
Outpatient	Reimbursement for transport costs	\$20 – \$100 per visit
Inpatient	Compensation for inconvenience of hospitalisation and incentive for participation	\$200 – \$500 per day

*The payment amount takes into consideration the current local standard of living (i.e. year 2021) and may be revised when necessary.*

#### **4.2.3 Applicable Fees for New Submissions**

For studies initiated by staff from NHG or partner institutions, there is no direct charge for ethics review.

For studies sponsored by the industry or commercial entities, review fees will apply for initial applications.

*Please refer to the following website for the latest review fees  
<https://www.research.nhg.com.sg> > Research Ethics Framework > DSRB Announcements.*

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## **4.3 Review of Submitted Applications**

### **4.3.1 Categories of Review**

The PI should select the appropriate ROAM application form for their study:

- DSRB application form 1 – Non-Exempt category  
 This category is for the submission of all Expedited review and Full Board review studies.
- DSRB application form 2 – Exempt category  
 This category is for the submission of all Exempt review studies.

All research studies submitted to the DSRB will be classified under one of the following review categories:

- I. Exempt Review
- II. Expedited Review
- III. Full Board Review

The determination of the review category is made by the DSRB. In general, the determination is based on the level of risk in which research participants are exposed to. Research studies that involve minimal or less than minimal risk are reviewed under the Exempt or Expedited review categories, and studies that involve more than minimal risk are reviewed under the Full Board review category.

### **I. Exempt Review**

This category is for the review of research studies that involve anonymous surveys and questionnaires, collection or study of anonymous existing data or tissue specimens, where data / tissue are either publicly available or subjects cannot be identified, or public benefit programmes. These studies will be reviewed by the chairperson or deputy chairperson of the relevant DSRB domain.

Research activity that falls under any of the following categories may qualify for exemption status.

#### **EXEMPTION CATEGORY 1 – Normal Educational Practices and Settings**

Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:

- a. Research on regular and special education instructional strategies; or
- b. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Research will qualify for exemption under this category if **all** the following are met:

- i. All of the research is conducted in a commonly accepted educational setting (e.g., a private or public school).
- ii. The research involves normal educational practices (e.g. comparison of instructional techniques).
- iii. The study procedures do not entail a significant deviation in time or effort from those educational practices already existent at the study site.
- iv. The study procedures do not involve an increase in the level of risk or discomfort beyond normal, routine educational practices, including physical education.
- v. The study procedures do not involve deception or withholding of information.

- vi. The study procedures do not involve sensitive topics, such as sexual behavior of individual participants or population. A sensitive survey is one that deals with socially questionable or highly personal issues or alcohol and/or drug abuse.
- vii. Provisions are made to ensure the existence of a non-coercive environment for all students, including those who choose not to participate.
- viii. The school or other agency grants written approval for the research to be conducted.
- ix. Educational tests of (i) knowledge, (ii) mastery, or (iii) skills.

#### EXEMPTION CATEGORY 2 – Anonymous Educational Tests, Surveys, Interviews or Observations

Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observations of public behaviour, unless:

- a. Information obtained is recorded in such a manner that human participants can be identified, directly or indirectly through identifiers linked to the participants;
- b. Any disclosure of the human participants' responses outside of the research could reasonably place participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation.

#### EXEMPTION CATEGORY 3 – Identifiable Participants in Special Circumstances

Research involving the use of educational tests, (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behaviour that are not exempted under Exemption Category 2, if:

- a. The human participants are elected or appointed public officials or candidates for public office; or
- b. Statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

#### EXEMPTION CATEGORY 4 – Collection of Existing Data

Research involving the study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that participants cannot be identified, directly or through identifiers linked to the participants. The reviewed material should be in existence at the time the research is proposed and should not be prospectively collected.

#### EXEMPTION CATEGORY 5 – Public Benefit or Service Programmes

Research and demonstration projects which are conducted by or participant to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

- a. Public benefit or service programmes;

- b. Procedures for obtaining benefits or services under those programmes;
- c. Possible changes in or alternatives to those programmes or procedures;
- d. Possible changes in methods or levels of payment for benefits or services under those programmes.

Research will qualify for exemption under this category if all the following are met:

- i. The research or demonstration project is conducted pursuant to specific federal statutory authority.
- ii. There is no statutory requirement for IRB review of the project.
- iii. The project does not involve significant physical invasions or intrusions upon the privacy of participants.
- iv. The exemption is authorized by the federal funding agency.
- v. The program under study delivers public benefit or service (e.g., financial or medical benefits) or service (e.g., social, supportive, or nutritional services).

#### **EXEMPTION CATEGORY 6 – Taste and Food Evaluation and Acceptance Studies**

Taste and food quality evaluation and consumer acceptance studies:

- a. If wholesome foods without additives are consumed; or
- b. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe.

#### **Special Circumstances**

The criteria for exemption do not apply for:

- a. Research involving prisoners;
- b. Research involving children, when the research involves survey or interview procedures or observations of public behaviour (except when the investigator(s) do not participate in the activities being observed);
- c. FDA-regulated research.

## **Exempt Review Determination**

The determination of whether a research study meets the criteria for Exempt review is made by the DSRB. Should the DSRB secretariat determine that an application does not qualify for exemption or if modifications are required, such as submission of a consent document or strengthening of protections in place to minimize risks to participants, the PI will be informed to re-submit the research proposal using the Non-Exempt application form, and the study will be scheduled for Expedited or Full Board review.

## **II. Expedited Review**

Research studies that involve collection of data or biological samples via non-invasive procedures, medical case-notes review, surveys or interviews with identifiers, may qualify for Expedited review. These studies will be reviewed by the chairperson or deputy chairperson of the relevant DSRB domain.

The Expedited review process may be used for:

- a. Initial review of new research proposals;
- b. Continuing review;
- c. Review of study amendments;
- d. Review of modifications requested by DSRB to secure approval (conditional approval).

The DSRB will determine if a proposed research study qualifies for a review by the expedited process. To qualify for such, a research proposal must meet the following criteria:

- a. The research proposal presents no more than minimal risk to research participants;
- b. Identification of participants and / or their responses does not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatising, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal;
- c. The research is not classified;
- d. The research activity is in one of the categories of research listed below.

**EXPEDITED CATEGORY 1** – Clinical studies of drugs and medical devices only when one of the following is met:

- a. Research on drugs for which an investigational new drug application is not required; or

- b. Research on a medical device for which an investigational device exemption application is not required or the medical device is cleared / approved for marketing and the medical device is being used in accordance with its cleared / approved labelling.

**EXPEDITED CATEGORY 2** – Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

- a. From healthy, non-pregnant adults who weigh at least 50 kg. For these participants, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week.
- b. From other adults and children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
- c. For collection of blood samples that do not fulfil the two criteria above, the research study will undergo a Full Board review.

**EXPEDITED CATEGORY 3** – Prospective collection of biological specimens for research purposes by non-invasive means. Examples:

- a. Hair and nail clippings in a non-disfiguring manner;
- b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
- c. Permanent teeth if routine patient care indicates a need for extraction;
- d. Excreta and external secretions (including sweat);
- e. Uncannulated saliva collected either in an un-stimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue;
- f. Placenta removed at delivery;
- g. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labour;
- h. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
- i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings,
- j. Sputum collected after saline mist nebulisation.

EXPEDITED CATEGORY 4 – Collection of data through non-invasive procedures (not involving general anaesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must have been approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for Expedited review, including studies of cleared medical devices for new indications).

Examples:

- a. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subjects or an invasion of the subject's privacy;
- b. Weighing or testing sensory acuity;
- c. Magnetic resonance imaging without contrast;
- d. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography,
- e. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

EXPEDITED CATEGORY 5 – Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

EXPEDITED CATEGORY 6 – Collection of data from voice, video, digital, or image recordings made for research purposes.

EXPEDITED CATEGORY 7 – Research on individual or group characteristics or behaviour (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behaviour) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

### **III. Full Board Review**

Research studies that do not qualify for the Exempt or Expedited review categories will be reviewed by the Full Board. In general, research studies that involve more than minimal risk will undergo Full Board review. Such studies may include research studies that are studying the safety and efficacy of a medicinal product or medical device, or research studies that involve invasive procedures.

For studies involving the collection of blood samples by finger stick, heel stick, ear stick or venipuncture, the following criteria specify the maximum allowable blood volume that may be drawn from subjects:

- a. From other adults, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected, not more than 5% of Total Blood Volume may be drawn over 24 hours, with a maximum amount of 500ml on a single withdrawal of blood.
- b. From other children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected, not more than 3% of Total Blood Volume may be drawn over 24 hours, with a maximum amount of 200ml on a single withdrawal of blood.
- c. If the maximum amount of blood is withdrawn from a subject, no subsequent blood should be drawn for 3 months.
- d. From healthy, non-pregnant adults who weigh at least 50 kg, the allowable maximum amount of blood drawn will be assessed and determined by the Full Board committee.

Table 15 below may be used as a guideline for determining the maximum allowable blood volume that may be drawn in studies subject to Full Board review.

Table 15: Maximum allowable total blood draw volumes (clinical & research)

<b>Body Weight (Kg)</b>	<b>Body Weight (lbs.)</b>	<b>Total Blood Volume (mL)</b>	<b>Maximum Allowable Volume (mL) for Children ( = 3% of total blood volume) drawn in a 90-day period</b>	<b>Maximum Allowable Volume (mL) for Adults ( = 5% of total blood volume) drawn in a 90-day period</b>
1	2.2	100	3	5
2	4.4	200	6	10
3	6.3	240	7.2	12
4	8.8	320	9.6	16
5	11	400	12	20
6	13.2	480	14.4	24
7	15.4	560	16.8	28
8	17.6	640	16	32
9	19.8	720	19.2	36
10	22	800	24	40
11-15	24-33	880-1200	26.4-36	44-60
16-20	35-44	1280-1600	38.4-48	64-80
21-25	46-55	1680-2000	50.4-60	64-100
26-30	57-66	2080-2400	62.4-72	104-120

31-35	68-77	2480-2800	74.4-84	124-140
36-40	79-88	2880-3200	86.4-96	144-160
41-45	90-99	3280-3600	98.4-108	164-180
46-50	101-110	3680-4000	110.4-120	184-200
51-55	112-121	4080-4400	122.4-132	204-220
56-60	123-132	4480-4800	134.4-144	224-240
61-65	134-143	4880-5200	146.4-156	244-260
68-70	145-154	5280-5600	158.4-168	264-280
71-75	156-185	5680-6000	170.4-180	284-300
76-80	167-176	6080-6400	182.4-192	304-360
81-85	178-187	6480-6800	194.4-204	324-340
86-90	189-198	6880-7200	206.4-216	344-360
91-95	200-209	7280-7600	218.4-228	364-380
96-100	211-220	7680-8000	230.4-240	384-400

Chart adapted from:

Committee on Clinical Investigations, Children's Hospital in Los Angeles, CA; Baylor College of Medicine, Dallas, TX; and Cincinnati Children's Hospital Institutional Review Board, OH.

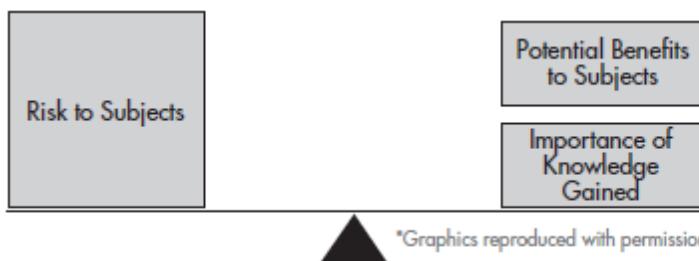
For further details on how to complete the ROAM application form, please refer to the ROAM guidebooks at <https://www.research.nhg.com.sg> > Resources > ROAM Guides.

#### 4.3.2 Review Considerations and Criteria

##### Risk-Benefit Assessment

The anticipated benefit, either to new knowledge or improved health of subjects should justify the risk to subjects in taking the risk to participate in the research study.

Figure 2: Benefit-risk ratio

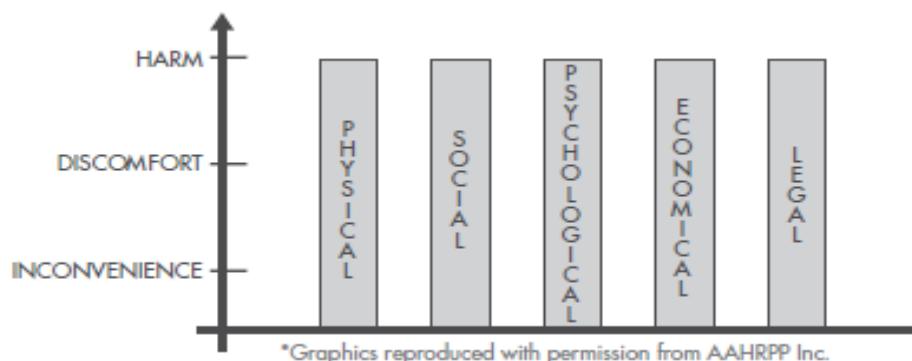


\*Graphics reproduced with permission from AAHRPP Inc.

The different risks to which subjects may be exposed to can be classified as follows:

- a. Physical – e.g. bruising after blood draw, study drug related adverse events;
- b. Psychological – e.g. psychological effects following survey asking sensitive questions;
- c. Social – e.g. breaches in confidentiality revealing that a subject suffers from a psychiatric illness;
- d. Economic – e.g. additional expenses to be borne by subject due to participation in research;
- e. Legal – e.g. mandatory reporting of drug abuse discovered during the research may cause legal problems for the subject.

Figure 3: Research-related risks

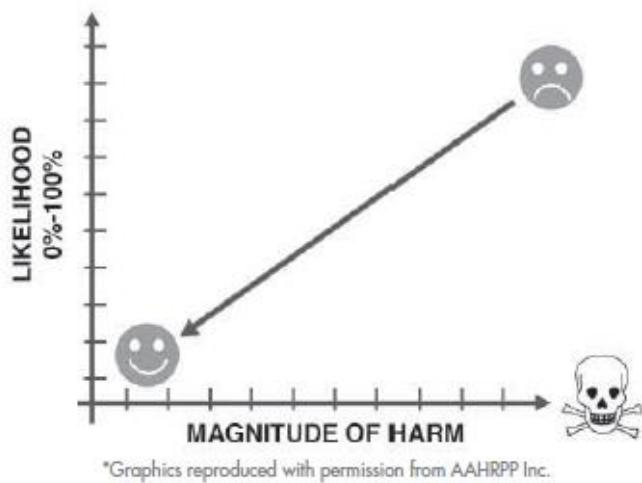


Only research-related risks should be considered, while risks associated with treatment that the subject would undergo even if not participating in the research and disease progression need not be considered while assessing research related risks.

**MINIMAL RISK** is defined as “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests”.

The PI should constantly strive to minimise both the magnitude of harm as well as the likelihood of the risk.

Figure 4: Likelihood of risk versus magnitude of harm to subjects



**MAGNITUDE** – Risks may range from a mere inconvenience (such as an extra visit to the clinic) to a serious harm or even death.

**LIKELIHOOD** – The probability of occurrence of the risk. Some examples of the ways the investigator can minimise risks are:

- a. Physical – Procedures already being performed on the research subjects for diagnostic or treatment purposes should be used, instead of performing additional tests for research. For example, drawing extra blood during a routine blood draw for treatment rather than drawing blood specifically for research;
- b. Psychological – Debriefing after the completion of the research;
- c. Social – Ensuring confidentiality is maintained especially while dealing with sensitive information;
- d. Economic – Ensuring that the subject does not have to pay out of pocket for research-related expenses and that institution covers treatment for research-related injuries;
- e. Legal – Informing the subject during consent process if mandatory reporting is required or employing a study design that assures anonymity;

In the event of UPIRTSOs/Expected SAEs, the PI is responsible for the following:

- a. Management of the event – The PI should ensure that adequate medical care is provided to the subject for treatment of adverse events.
- b. Assessment of the event – The PI should assess the risk, expectedness, and relation of the event to the study.
- c. Reporting of the event – The PI must report the event to the DSRB, and where applicable, to other relevant authorities.

*For more information on UPIRTSOs, please refer to chapter 4.7 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) and Expected Serious Adverse Event (SAE).*

## **Review Criteria**

All research proposals that intend to enrol human participants must meet certain criteria before study procedures can be initiated. The criteria are based on the principles of respect for persons, beneficence and justice as discussed in the Belmont Report.

In general, a research study (including new applications, study amendments and continuing reviews) must fulfil the following minimum criteria for ethics approval:

- a. Risks are minimised, and are reasonable in relation to anticipated benefits;
- b. Selection of participants are equitable;
- c. Informed consent will be sought, and appropriately documented;
- d. Adequate provision for monitoring of data to ensure safety, protection or privacy or research participants and confidentiality of data collected;
- e. Additional protection for vulnerable populations.

In administering the above review criteria, the DSRB will consider the following elements of review:

- a. Risks to subjects are minimised by using procedures which are:
  - i. Consistent with sound research design;
  - ii. Do not unnecessarily expose subjects to risk; and
  - iii. When appropriate, already being performed for diagnostic or treatment purposes.
- b. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result:
  - i. The DSRB will consider only those risks and benefits that may result from the research (as distinguished from the risks and benefits of therapies subjects would receive even if not participating in the research).
  - ii. The DSRB will not consider possible long-range effects of applying knowledge gained in the research as among those research risks (such as possible effects of the research on public policy) that fall within the purview of its responsibility.
- c. Selection of subjects is equitable – In making this assessment, the DSRB will take into account the following:

- i. The purposes of the research;
  - ii. The setting in which the research will be conducted;
  - iii. Special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
- d. Informed consent will be sought from each prospective subject or the subject's legal representative, in accordance with, and to the extent described in chapter 5.0 Informed Consent and chapter 6.1 Research Involving Children.
- e. Informed consent will be appropriately documented, in accordance with, and to the extent described in chapter 5.0 Informed Consent.
- f. When appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.
- g. When appropriate, there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.
- h. When some or all of the subjects are likely to be vulnerable to coercion or undue influence – such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons – additional safeguards have been included in the study to protect the rights and welfare of these subjects.
- i. The HBRA prohibits the commercial trading of human tissue (whether for research, therapy or any other purpose). Therefore, the DSRB will not approve any research that involves the use of human tissues that are purchased commercially.

*For more information on vulnerable subjects, please refer to chapter 6.0 Research in Vulnerable Populations.*

## **4.4 Outcome of Review**

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Following the review of a research proposal, the DSRB must reach one of the following decisions:

- a. Approved
- b. Conditionally approved
- c. Tabled for next convened meeting
- d. Not approved

The DSRB may make one of the following determinations as a result of its review of the research submitted for initial review, continuing review or study amendments:

- a. APPROVED – The research proposal is approved as submitted. The PI is not required to change any aspect of the proposal or consent document.
- b. CONDITIONALLY APPROVED – There are no major problems with the study. If the PI addresses the issues listed by the DSRB, the study can be formally approved. Participants must not be recruited into the study until the final approval has been issued.
- c. TABLED FOR NEXT CONVENED MEETING – A proposal may be tabled if there are significant questions raised that need further information from the PI. The DSRB decides on the subsequent action required. The PI may be asked to submit additional information, be invited to attend a subsequent meeting, or the proposal might be sent to an independent consultant for further review. When the additional information has been obtained, the proposal is discussed at the next DSRB meeting.
- d. NOT APPROVED – The proposal fails to meet one or more criteria used by the DSRB for the approval of research. Disapproval cannot be given through the expedited review mechanism and may only be given by majority vote at a convened meeting of the DSRB.

#### **4.4.1 Appeals Against DSRB Decisions**

The PI shall have an opportunity to respond in writing to the DSRB if a submitted research activity is not approved. The DSRB will give the PI's appeal a careful and fair evaluation.

- a. If the DSRB determines that a study is not approved, it provides the reasons for the disapproval, in writing to the PI.
- b. The PI may appeal against the DSRB's decision by responding to the DSRB Chairperson (through the DSRB Secretariat) within 30 calendar days upon receiving the outcome.
- c. In the PI's appeal, he/she should include the rationale for the appeal (with supporting documents where relevant), and documentation from the Institutional Representative (IR) or designee that supports the PI's decision to appeal.
- d. Upon receipt of the PI's appeal, the DSRB secretariat will forward the appeal to the REC Chairperson or designee to determine if the PI's appeal should be directed to:
  - i. The same DSRB to reconsider and review its decision; or
  - ii. The REC for a second initial review.
- e. If the REC Chairperson or designee has determined that the PI's appeal should be directed to the same DSRB for review, then the DSRB Secretariat will add the PI's appeal to the next scheduled DSRB meeting agenda and notify the PI of the DSRB meeting date.

- f. If the REC Chairperson or designee has determined that the PI's appeal should be directed to the REC for review, then the REC Secretariat will add the PI's appeal to the next scheduled REC meeting agenda. If this is more than a month away, the REC Secretariat will arrange for an ad-hoc REC meeting. The REC Secretariat will notify the PI of the REC meeting date.
- g. Once the PI's appeal has been placed on the DSRB / REC agenda, the PI will be notified and will be given the opportunity to attend the meeting and present information in person. Copies of the PI's response will be provided to all members of the DSRB / REC with their regular meeting review materials.
- h. If the study is directed to the REC for a second initial review, then the Chairperson of the DSRB which first reviewed the study shall not participate in the deliberation and voting, but may provide information as requested by the REC.
- i. The DSRB / REC will carefully and fairly evaluate the PI's appeal in reaching its final decision. The DSRB / REC Secretariat will notify the PI of the DSRB's / REC's final decision. If the study is disapproved, this letter will include the reason(s) for the disapproval.
- j. The DSRB's / REC's decision is final. The PI cannot appeal further against this decision.
- k. If the study is directed to the REC for a second initial review, then the REC Chairperson shall endorse the letter that communicates the outcome to the PI. If the study is approved, the initial reviewing DSRB shall continue to oversee and review the subsequent submissions (e.g. study amendments, UPIRTSOs etc.).
- l. All PIs are encouraged to contact the DSRB to provide other types of feedback. However, other types of investigator feedback are accepted without this process.

## **4.5 Study Amendments**

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No deviation from, or changes to, the approved study/ protocol should be implemented without documented approval from the DSRB, except where necessary to eliminate apparent immediate hazard(s) to the study participants.

Any deviation from, or a change of, the approved study/ protocol to eliminate an immediate hazard should be documented and promptly reported to the DSRB via the ROAM Non-Compliance / Study Deviation Form within 7 calendar days.

*For more information, please refer to chapter 4.8 Non-Compliances / Study Deviations.*

It should be noted that a change of PI and / or changes in specific study team member roles (e.g. from Collaborator to Co-Investigator) should also be submitted as a study amendment.

*For more information, please refer to chapter 3.4 Change of PI and / or Study Team Members.*

#### **4.5.1 Supporting Documents for Study Amendments**

A study amendment submission must include (but is not limited to) the following:

- a. A duly completed ROAM Study Amendment Cover Note (including summary and rationale of amendments);
- b. Amended documents (both tracked and clean versions);
- c. Any other documentation that the DSRB may specifically request; and
- d. Any other relevant documentation to be given to subjects when, in the judgment of the DSRB, the additional information would add meaningfully to the protection of the rights, safety and / or well-being of the subjects.

#### **4.5.2 Review Categories for Study Amendments**

The submitted amendments will be categorised according to the following definitions:

- a. Administrative amendments – Administrative changes such as change in addresses, contacts, etc., and correction of typographical and grammatical errors fall into this category which will be reviewed and acknowledged by the DSRB Secretariat. The DSRB Secretariat will send an acknowledgment letter to the PI to indicate receipt of the administrative amendments.
- b. Minor amendments – The DSRB Secretariat will determine if the changes to the protocol affect the risk-benefit ratio of the study. Changes to the protocol that pose any increase in risk which are not more than minimal risk or new procedures added that fit within the categories eligible for expedited review, will fall into this category.
- c. Major amendments – The DSRB Secretariat will determine if the changes to the protocol affect the risk-benefit ratio of the study. Amendments that significantly affect the risk-benefit ratio will undergo a Full Board review.

Some examples of changes that would require a Full Board review include (but are not limited to):

- a. Changes to the inclusion and / or exclusion criteria that significantly alter the risk-benefit ratio;
- b. Major changes to the ICF or process that increases the overall risk to the participants involved in the study;
- c. Addition of any study procedures that are of greater than minimal risk;
- d. Increase in study participants for a study previously reviewed by Full Board review;

- e. Alterations to the drug dose or delivery;
- f. Any other type of amendment to the study that in the opinion of the DSRB should be reviewed at a Full Board meeting.

#### **4.5.3 Applicable Fees for Study Amendments**

For studies initiated by staff from NHG or partner institutions, there is no direct charge for ethics review.

For studies sponsored by the industry or commercial entities, review fees will apply for study amendment submissions.

*Please refer to the following website for the latest review fees*  
<https://www.research.nhg.com.sg> > Research Ethics Framework > DSRB Announcements.

### **4.6 Continuing Review**

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Continuing review is required by the DSRB as long as the study is collecting individually identifiable data. All research studies submitted for Expedited review and Full Board review at the initial submission will be required to undergo a continuing review by DSRB at the end of the specified study approval period. Research studies reviewed via the Exempt route at initial submission are not required to undergo continuing review submissions.

The DSRB will conduct continuing review of ongoing research (except studies reviewed via the Exempt route) at intervals appropriate to the degree of risk, which is determined at the initial review. Continuing reviews are conducted at least once per year, but the frequency of review may be increased if the degree of risk is higher. Unless the DSRB determines otherwise, continuing review is not required for research that has progressed to the point that it only involves data analysis, including analysis of individually identifiable private information and/or individually identifiable biospecimens (*refer to Special Considerations under Section 4.6.3*).

If the study approval expires, no research activities, including recruitment, advertising, screening, enrolment, interventions, interactions and collection of identifiable data can occur after the expiry date, unless specific permission is granted by the DSRB.

The PI should submit a completed ROAM Study Status Report Form at least 4-6 weeks before the study approval period ends (as indicated in the approval letter of the study).

#### **4.6.1 Supporting Documents for Continuing Review**

The PI applying for renewal of approval of a study must submit:

- a. A duly completed ROAM Study Status Report Form (see section 4.6.3 below);

- b. DSMB reports or any interim analysis reports;
- c. Any other documentation that the DSRB may specifically request.

#### **4.6.2 Review Categories for Continuing Review**

Studies submitted for continuing review may be reviewed via the Expedited route or Full Board route. (Studies reviewed under the Exempt route at the initial submission will not require continuing review.)

To qualify for review by Expedited route at continuing review, the research must meet the following criteria:

The research is not classified, and the research activities involve procedures listed in one or more of the Expedited Review categories 1 to 7 (please refer to section 4.3.1 Categories of Review, sub-section II on Expedited Review), or involve procedures fulfilling category 8 or 9 as defined below.

**EXPEDITED REVIEW CATEGORY 8A** – Continuing review of study can be conducted by expedited process under this category if all the following have been met:

- a. The research is permanently closed to new participants;
- b. All participants have completed all research-related interventions; and
- c. The research remains active only for long-term follow-up of participants.  
(For a multi-centre study, the Expedited review procedure may be used by DSRB when all of the above are satisfied for NHG or partner institution sites.)

**EXPEDITED REVIEW CATEGORY 8B** – Continuing review of study can be conducted by expedited process under this category if all the following have been met:

- a. No participants have been enrolled – i.e. no participants have ever been enrolled into the study at NHG or partner institution sites; and
- b. No additional risks have been identified.

**EXPEDITED REVIEW CATEGORY 8C** – Continuing review of study can be conducted by expedited process under this category if all the following have been met:

- a. Where the remaining research activities are limited to data analysis.

#### **EXPEDITED REVIEW CATEGORY 9**

- a. The research is not conducted under an IND or IDE;
- b. The DSRB has determined and documented at a Full Board meeting that:

- i. The research involves no greater than minimal risk; and
- ii. No additional risks have been identified.

All other studies submitted for continuing review that do not meet the Expedited review criteria as detailed above will undergo a Full Board review.

#### **4.6.3 Study Status Reporting.**

A duly completed ROAM Study Status Report Form must indicate the status of the study, details of each as follows:

- a. **NOT YET INITIATED** – No research-related activities have been performed since first approval. The PI must provide reasons for why the study has yet to be initiated.
- b. **ONGOING** – Research-related activities are still being performed.
- c. **ENROLMENT CLOSED, SUBJECTS ON FOLLOW UP ONLY** – The study is permanently closed to new participants, all participants have completed research-related interventions, and the research remains active only for long-term follow-up.
- d. **LAST PATIENT LAST VISIT OVER, DATA ANALYSIS ONGOING** – There will be no more contact with participants and the remaining research activities are limited to data analysis.
- e. **COMPLETED** – There will be no more research activities, including contact with participants or any data analysis. The PI must indicate the completion date.
- f. **SUSPENDED / TERMINATED** –
  - i. Sponsor-imposed termination / suspension: A determination from the sponsor of the study to terminate a research study or place a specific research study on hold. This determination may be made for interim data analysis, inadequate drug availability, response to a DSMB report / recommendation, or a pre-planned stopping point. The PI will be required to provide the reason for this status.
  - ii. Termination / suspension by PI: A determination from the PI of the study to terminate a research study or place a specific research study on hold. This determination may be made for interim data analysis, inadequate drug availability, response to a DSMB report / recommendation, or a pre-planned stopping point. The PI will be required to provide the reason for this status.

For multi-centre studies, the PI can indicate a different site status for each of the study sites.

*For more information on the procedures related to changes in the status of a research study, please refer to chapter 4.9 Changes in Study Status.*

## **Special Considerations for Studies with Ongoing Data Analysis**

With effect from 15 Aug 2018, unless otherwise determined by the DSRB, studies that have submitted a Study Status Report Form (SRF) whereby the study status is “Last Participant, Last Visit Over & Only Data Analysis Ongoing” will be exempted from continuing review once the SRF has been approved.

However, if amendments are made to the study which changes the study status such as that it no longer involves data analysis only (e.g. collection of additional data), the PI must submit a new SRF to update the DSRB of the new study immediately, and continuing review will be required.

The PI is still expected to report non-compliances, UPIRTSOs and other important notifications to the DSRB. They must also submit a SRF to inform DSRB when the study is considered completed or is terminated.

### **4.6.4 Criteria for Continuing Review**

In performing a continuing review, the DSRB takes into consideration the following information about the progress of the study:

- a. Subjects recruitment;
- b. Number and reasons for withdrawal of subjects;
- c. UPIRTSOs, including SAEs since the last review;
- d. Expected Serious Adverse Event (SAE) for Human Biomedical Research (HBR), since last review
- e. Study Amendments since the last review;
- f. Assessment of the current risk, potential benefits, and the overall risk / benefit ratio of the study;
- g. Research findings;
- h. Complaints about the research;
- i. Non-compliance reports,
- j. Any other relevant information, especially information about the risks associated with the research.

## **4.7 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) and Expected Serious Adverse Event (SAE)**

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### **4.7.1 Definitions**

**ADVERSE EVENT** – Any untoward or unfavourable medical occurrence in a patient or clinical investigation subject administered with a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

**UPIRTSO** – A problem that is (1) unexpected (2) related or possibly related and (3) suggests that the research places subjects or others at greater risk of harm.

**SAE** – A serious adverse event or reaction is any untoward medical occurrence which:

- a. Results in or contributes to death;
- b. Is life-threatening;
- c. Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- d. Results in or contributes to persistent or significant disability or incapacity; or
- e. Results in or contributes to a congenital anomaly or birth defect.

**UNEXPECTED SERIOUS ADVERSE DRUG REACTION (USADR)** – A serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure, local product information leaflet).

### **4.7.2 Reportable Events**

The PI is responsible for the accurate documentation, investigation, follow-up and timely reporting of all UPIRTSOs and SAEs.

**(1) UPIRTSO** – Events that are (1) unexpected and (2) related or possibly related to study have to be reported to the DSRB. Table 16 below provides a summary of the types of UPIRTSOs that require reporting to the DSRB, as well as their respective reporting timelines.

Table 16: Summary of UPIRTSO reporting requirements

Risk Profile of study	More Than Minimal Risk (Reviewed via Full Board)	No More Than Minimal Risk (Reviewed via Expedited / Exempt)	Regardless of Risk Profile	Regardless of Risk Profile
Event / Problem	*Local death	*Local death	Life-threatening problems not	All other problems

			resulting in death	
<b>Description of Event / Problem</b>	Regardless of expectedness and causality	Must be related / possibly related to the study and regardless of expectedness	Unexpected and related / possibly related to the study	Unexpected and related / possibly related to the study
<b>Timeline for Initial Report</b>	Soonest possible but not later than 7 calendar days after first knowledge	Soonest possible but not later than 7 calendar days after first knowledge	Not later than 7 calendar days after first knowledge	Not later than 15 calendar days after first knowledge
<b>Timeline for Follow-Up Report</b>	Within 8 calendar days of initial report	Within 8 calendar days of initial report	Within 8 calendar days of initial report	-

\*Local is defined as occurrence in institutions under the oversight of the NHG DSRB.

More details on the UPIRTSO reporting requirements are described in the following sections.

### Assessment of Events

The PI must make a judgment about the expectedness, of an event. If the event is an adverse event, the PI must make a judgment about the causality of the adverse event. The PI must also analyse the event and state whether protocol / consent form revisions are required.

**ASSESSMENT OF EXPECTEDNESS** – The PI must state whether the event is expected or unexpected. An unexpected event is one, where the nature and severity of which is not consistent with information in the relevant source document (s). For a medicinal product not yet approved for marketing in Singapore, the Investigator’s Brochure will serve as the source document. Reports that add significant information on specificity or severity of a known, already documented serious adverse event constitute unexpected events. For example, an event more specific or more severe than described in the Investigator’s Brochure would be considered unexpected. An unexpected event is also one that is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the event and the participant’s predisposing risk factor profile for the event.

**ASSESSMENT OF CAUSALITY** – The PI should evaluate the event and assess causality. The expression ‘reasonable causal relationship’ is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. For purposes of reporting, adverse event reports associated with marketed drugs usually imply causality. The following conditions might help to assess causality:

- a. The event has a reasonable temporal relationship to the intervention.
- b. The event could not have been produced by the underlying disease states.

- c. The event could not have been due to other non-study interventions.
- d. The event follows a known pattern of response to the intervention.
- e. The event disappears with cessation of intervention.

**ASSESSMENT OF SERIOUSNESS** - A serious adverse event or reaction is any untoward medical occurrence that:

- a. results in or contributes to death,
- b. is life threatening,
- c. requires inpatient hospitalisation or prolongation of existing hospitalisation,
- d. results in or contributes to persistent or significant disability / incapacity,
- e. results in or contributes to a congenital anomaly or birth defect, or
- f. results in such other event as may be prescribed.

### **Examples of Reportable Events**

- a. Adverse event (any harm experienced by a subject regardless of whether the event was internal (on-site) or external (off-site) and regardless of whether the event meets the FDA definition of “serious adverse event”), which in the opinion of the PI are both unexpected and related.
  - i. An unexpected adverse event is one, where the nature and severity of which is not consistent with information in the relevant source documents.
  - ii. An adverse event is “related to the research procedures” when there are facts (evidence) or arguments to suggest a causal relationship.
- b. Information that indicates a change to the risks or potential benefits of the research. For example:
  - i. An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the DSRB.
  - ii. A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the DSRB.
- c. A breach of confidentiality.
- d. Change in FDA labelling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

- e. Change to the protocol taken without prior DSRB review to eliminate an apparent immediate hazard to a research subject.
- f. Incarceration of a subject in a protocol not approved to enrol prisoners.
- g. Event that requires prompt reporting to the sponsor.
- h. Sponsor imposed suspension for risk.
- i. Complaint of a subject when the complaint indicates unexpected risks or cannot be resolved by the research team.
- j. Protocol violation (meaning an accidental or unintentional change to the DSRB approved protocol) that harmed subjects or others or that indicates subjects or others may be at increased risk of harm.
- k. Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application [including a supplementary plan or application], or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).

## **(2) Expected SAE (only for HBRA-regulated studies)**

Expected SAE(s) reportable to DSRB are events that are (1) expected (2) serious (3) related to the HBR study.

Both local and overseas expected SAE(s) should be reported. For example, for multi-centre HBR studies involving collaborations from local and overseas research sites for the same research protocol, any expected SAE which occurs in a participant during the research at the overseas site must also be reported to the DSRB.

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.

### **4.7.3 Reporting Timelines**

The PI is responsible for the timely reporting of the reportable problems to the DSRB.

## **(1) UPIRTSO**

For the purposes of the reporting of local deaths as described below, “local” is defined as being under an NHG institution, or an institution under the oversight of NHG DSRB.

**FOR MORE THAN MINIMAL RISK** (i.e. Full Board review) STUDIES - All problems involving local deaths should be reported as soon as possible, but not later than 7 calendar days after first knowledge by the investigator, regardless of causality and expectedness of the death event. Any additional relevant information about the death should be reported within 8 calendar days of making the initial report.

**FOR NO MORE THAN MINIMAL RISK** (i.e. Exempt or Expedited Review) STUDIES - Only problems involving local deaths that are related or possibly related to the study should be reported as soon as possible, but not later than 7 calendar days after first knowledge by the investigator. Any additional relevant information about the death should be reported within 8 calendar days of making the initial report.

Problems which are life threatening should be reported as soon as possible, but not later than 7 calendar days after first knowledge by the investigator. Any additional relevant information about the problems should be reported within 8 calendar days of making the initial report.

All other problems must be reported as soon as possible but not later than 15 calendar days after first knowledge by the investigator.

## **(2) Expected SAE (only for HBRA-regulated studies)**

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

### **4.7.4 Reporting Requirements for Local Deaths in Oncology Studies**

A separate set of reporting requirements apply for local deaths occurring in oncology studies, where:

- a. Most of such deaths occur when the subjects are in the treatment free follow-up phase (due to natural disease progression);
- b. The local death(s) is / are unrelated to the investigational product;
- c. The local deaths yield no clinically meaningful information that allows assessment of the risk-benefit relationship of the study,
- d. There are no significant implications on the rights and welfare of the subjects.

The reporting requirements for local deaths in oncology are detailed in table 17 below.

*Table 17: Reporting requirements for local deaths in oncology studies*

<b>Local Death Occurring Within 60 Days (or Less) After Last Dose of Treatment</b>	<b>Local Death Occurring More Than 60 Days After Last Dose of Treatment</b>
Related (expected or unexpected)  <i>Preliminary report by PI within 7 calendar days of first knowledge</i>	Related (expected or unexpected)  <i>Preliminary report by PI within 7 calendar days of first knowledge</i>
Unrelated (expected or unexpected)  <i>Preliminary report by PI within 7 calendar days of first knowledge</i>	Unrelated (expected or unexpected)  <i>Routine reporting for Annual Continuing Review</i>

The PI is required to follow up with the detailed report within 8 calendar days after the preliminary report. Wherever possible, all unrelated and expected local death reports should be reviewed by a data and safety monitoring entity.

#### **4.7.5 Adverse Event Reporting to the Sponsor and / or Regulatory Authorities**

The PI must report all SAEs to the sponsor (where applicable), except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. In addition, the PI must also report the adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluations, according to the reporting requirements and within the time periods specified to the sponsor according to the protocol.

For reports of deaths, the PI should supply the sponsor and the DSRB with any additional requested information (e.g. autopsy reports, medical reports, etc.).

In addition, the PI should follow any regulatory requirements related to the reporting of SAEs and USADRs to the appropriate regulatory authorities, e.g. HSA and / or MOH.

*For more information on the regulatory requirements for safety reporting, please refer to the following websites:*

*Human Biomedical Research Act 2015, Ministry of Health Singapore, available at <https://www.moh.gov.sg>> Policies & Guidelines > Legislation.*

*Guidance on expedited safety reporting requirements for clinical trials, available at <https://www.hsa.gov.sg> > Home >Clinical Trials > Guidance documents for clinical trials > Conducting clinical trials*

## **4.8 Non-Compliances / Study Deviations**

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### **4.8.1 Definitions**

All research conducted in institutions under the oversight of NHG DSRB, should be in compliance with the research proposal approved by the DSRB, with GCP, with DSRB requirements, institution requirements and applicable regulations. The PI is encouraged to self-report any non-compliances that arise during the conduct of the study.

**COMPLIANCE** is adherence to all the protocol-related / study-related requirements, GCP requirements, DSRB requirements, NHG PCR requirements and any applicable regulatory requirements.

**NON-COMPLIANCE** is a failure by an investigator or any study team member to abide by the DSRB policies and procedures, GCP guidelines or applicable regulations governing the protection of human subject research.

Some examples of non-compliance include (but are not limited to):

- a. Failure to obtain approval for research;
- b. Failure to obtain renewal of approval for research;
- c. Failure to obtain informed consent when required;
- d. Failure to file adverse event reports;
- e. Performing an unapproved research procedure;
- f. Performing research at an unapproved site;
- g. Failure to submit study amendments for review and approval;
- h. Failure to adhere to the approved protocol;
- i. Any other failure to adhere to regulations, policies and procedures related to research.

**SERIOUS NON-COMPLIANCE** is an act or omission to act that has the potential to increase the physical, psychological, safety, or privacy risk to research subjects.

**CONTINUING NON-COMPLIANCE** is a repeated pattern, act, or omission to act that suggests a future likelihood of reoccurrence of the non-compliance.

**STUDY DEVIATION** is an unplanned excursion from the study that is not implemented or intended as a systematic change.

- a. A study deviation could be a limited prospective exception to the protocol (e.g. agreement between sponsor and investigator to enrol a single subject who does not meet all inclusion

- / exclusion criteria). Like study amendments, deviations initiated by the investigator must be reviewed and approved by the DSRB and the sponsor prior to implementation, unless the change is necessary to eliminate an immediate hazard to the research subjects.
- b. A study deviation is also used to refer to any other unplanned instance(s) of study non-compliance, e.g. situations in which the investigator failed to perform tests required by the protocol, or failures on the part of subjects to complete scheduled visits as required by the protocol.

#### **4.8.2 Reporting of Non-Compliances / Study Deviations to the DSRB**

The DSRB encourages the reporting of non-compliances and / or study deviations by the PI, members of the research team or others. When a report of non-compliance / deviation is made by someone other than the PI, the confidentiality of the reporter will be maintained. The reporter's name will not be disclosed to the individuals involved in the complaint, unless disclosure is required to reconcile the situation.

The PI or any study team member may contact the DSRB secretariat if he / she wishes to report an alleged non-compliance that cannot be done appropriately via the ROAM Non-Compliance / Study Deviation Form. The reporter's name will not be disclosed.

The DSRB may receive an allegation or a report of non-compliance / study deviation by various channels, including:

- a. Voluntary notification by the PI;
- b. PI not responding to DSRB's queries / reminders for renewal;
- c. Information given by other staff within the institution;
- d. Information given by other members of the research team;
- e. Monitoring reports;
- f. Audit reports;
- g. Complaints from research subjects.

The non-compliance / deviation must be reported to the DSRB as soon as possible but not later than 14 calendar days after first knowledge by the investigator. Investigators are obliged to suspend their research immediately pending their report to the DSRB if the non-compliances / deviations are significant or will likely result in greater harm or greater likelihood of harm to the subjects.

#### **4.8.3 DSRB Review of Non-Compliance Reports**

If the non-compliance / study deviation is determined to be neither serious nor continuing, the DSRB Chairperson or designee will require the PI to provide an explanation and outline a corrective and / or preventive actions taken to avoid future occurrences of the non-compliance / study deviation. If the PI's reply is unsatisfactory, the report will be handled as a serious or continuing non-compliance / study deviation.

If the allegation of non-compliance / study deviation is determined to be serious or continuing, the DSRB will conduct an inquiry and provide an opportunity for the PI to respond in person at a convened meeting, informal conference or in writing.

#### **Outcome of DSRB Inquiry**

If the DSRB accepts the PI's explanation, the DSRB will inform the PI within 30 days of the DSRB's review of the PI's reply.

If the DSRB deems the PI's explanation to be unsatisfactory, or if the PI fails to respond within the stipulated timeframe, the DSRB will determine if the PI should remain eligible to continue to conduct research studies at institutions under DSRB's governance, and make a recommendation for further actions. These may include (but are not limited to):

- a. Request for a For Cause study review by RQM;
- b. Modification of the study protocol;
- c. Modification of the information disclosed during the consent process;
- d. Require additional information to be provided to past and/or current participants;
- e. Notifying current participants of relevant information (required when such information may relate to participants' willingness to be re-consented for continued participation in the research);
- f. Requiring current participants to be re-consent for continued participation;
- g. Modification of the continuing review schedule;
- h. Monitoring of the research and /or consent process;
- i. Suspension of the research and other related studies (where applicable);
- j. Termination of the research and other related studies (where applicable);
- k. Notify other relevant parties to determine investigation approach or sharing of information;
- l. Obtaining more information pending a final decision, including the reports from investigations conducted by external parties;
- m. Referral to other organisational entities (e.g. legal counsel, risk management, institutional official);

- n. Mandating that the investigator attend additional training programmes;
- o. Requiring the investigator to work with a senior researcher (mentor) for a period of time;
- p. Disqualifying the investigator from conducting any research for a period of time,
- q. Other actions appropriate to the context of the non-compliance.

#### **4.8.3.1 NHG RI Review and Notification to MOH of Reportable Events (Non-Compliance Reports (NCR), Expected and Unexpected Serious Adverse Events (SAE))**

**NOTE: Section 4.8.3.1 is only applicable to NHG researchers. For researchers from non-NHG institutions, please check with your RI / relevant institutional authority on the required submission and their respective processes and timelines.**

The NHG RI reviews all contraventions and the occurrences of non-compliance reports (NCR) and expected and unexpected serious adverse events (SAE) reported by NHG researchers via ROAM.

These reports will be reviewed by the PIC to determine if they are reportable to MOH. The review process for unexpected SAEs is similar to that of NCR (refer to 4.8.3 above), except for the MOH reporting timelines.

For reports which are determined to be reportable to MOH, the NHG RI will contact the study team to complete the reporting form for submission to MOH within 7 calendar days.

For reports which qualifies to be reported annually to MOH, the NHG RI will contact the study team to complete the reporting form for submission to MOH at the next annual Declaration of Compliance.

#### **4.8.4 Regulatory Reporting of Serious Breaches**

**BREACH** – Any change, divergence or departure from:

- a. The principles of GCP;
- b. The trial protocol agreed to by the sponsor, and approved by the IRB and HSA (as required); or
- c. The clinical trial regulations.

**SERIOUS BREACH** – A breach during a clinical trial which is likely to affect to a significant degree:

- a. The safety, or physical or mental integrity, of any subject of a clinical trial; or
- b. The scientific value of the clinical trial.

The PI is required to notify HSA in writing of any serious breach occurring during the clinical trial of any of the following, as soon as possible but no later than 7 days after becoming aware of the breach:

- a. The principles of GCP;
- b. The clinical trial protocol;
- c. Clinical trials regulations.

*For more information on regulatory notification of serious breaches (Guidance on notification of serious breach), go to <https://www.hsa.gov.sg> > Home >Clinical Trials > Regulatory Guidances > Guidance documents for clinical trials > Conducting Clinical trials.*

## **4.9 Changes in Study Status**

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### **4.9.1 Study Expiration and Lapses in DSRB Approval**

There is no grace period extending the conduct of research beyond the expiration date of DSRB approval. It is the responsibility of the PI to submit the ROAM Study Status Report for continuing review well before the expiration date, allowing ample time for DSRB review.

If the PI fails to submit the study status report for an active research project, or if the DSRB has not reviewed and approved the submitted study status report by the expiration date, the study will be considered lapsed.

No research activities, including recruitment, advertising, screening, enrollment, interventions, interactions, and collection of identifiable data can occur on the expiration date or after, until the continuing review application has been approved by DSRB, or unless the investigator determines that it is in the subjects' best interest to continue their participation in the research study and specific permission for this has been granted by the DSRB.

It will be considered a non-compliance if research activities are performed during the period of lapse in ethics approval, unless specific permission has been granted by the DSRB. If such non-compliance occurs, the PI must submit a ROAM Non-Compliance / Study Deviation Form to document the activities conducted during the lapse and provide an explanation for the non-compliance.

*For more information, please refer to chapter 4.8 Non-Compliances / Study Deviations.*

### **4.9.2 Study Suspension / Termination**

A study may be closed before completion, due to suspension or termination by the PI or other parties (such as the study sponsor, DSRB, regulatory authorities, or institution).

When a study is suspended or terminated by the PI / sponsor / institution / regulatory authorities, the PI should cite the reason for this status and submit a report to the DSRB within 7 days, via the ROAM Study Status Report Form.

## **I. Study Suspension / Termination by DSRB**

The DSRB may decide, at a convened meeting, to suspend or terminate a study that is not being conducted in accordance with the DSRB's requirements, or that has been associated with unexpected serious harm to the research subjects. In addition, the DSRB Chairperson or deputy chairperson may suspend or terminate a research study on an urgent basis, to eliminate immediate harm to subjects. This will be reported to the DSRB at the next convened meeting.

Some examples of situations when the DSRB may suspend or terminate a research study include (but are not limited to):

- a. Inappropriate involvement of human subjects in research;
- b. Infringement of the rights or welfare of participants;
- c. Serious or continuing non-compliance with the regulations or DSRB policies;
- d. Emergence of new information suggesting increased risk to human participants,
- e. Expiry of approval.

## **II. Study Reactivation Following Suspension**

The PI or sponsor may request to reactivate studies that have been put on hold by the PI / sponsor / DSRB. The request for reactivation will be reviewed either as a continuing review or as a new study submission based on the following considerations:

- a. Duration since suspension;
- b. Circumstances surrounding suspension;
- c. Enrolment status of the study;
- d. Level of risk involved in the study; and
- e. Any other issue(s) deemed significant by the DSRB.

### **4.9.3 Study Completion**

A research study is said to be completed when all of the following criteria have been fulfilled:

- a. The research is permanently closed to the enrolment of new participants.
- b. All participants have completed all research-related interventions.
- c. Collection and analysis of individually identifiable data has been completed.

When a study is completed, the PI should submit a study completion report within 30 days after completion of the study. Completion reports should be submitted using the ROAM Study Status Report Form.

The DSRB Secretariat will review the ROAM Study Status Report Form and obtain any outstanding information or documentation from the PI where necessary. If there are inconsistencies or if clarification is needed, the DSRB Secretariat will request for additional information.

## **4.10 Other Notifications**

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Miscellaneous documents relevant to the study may be submitted to the DSRB via the ROAM Other Notifications Form.

Some examples of documents that may be submitted to the DSRB using the ROAM Other Notifications Form include (but are not limited to):

- a. DSMB reports;
- b. Annual / interim / periodic safety reports;
- c. Study insurance documentation;
- d. Clinical trial agreements;
- e. Interim data analyses;
- f. Letters from study sponsors;
- g. Any other information that the PI or sponsor wishes to notify the DSRB about.

# **CHAPTER 5**

# **INFORMED CONSENT**

- 5.1 Important Considerations for the Informed Consent Process**
- 5.2 Developing the Informed Consent Form (ICF)**
- 5.3 Study Team Members Authorised to Take Consent**
- 5.4 Documentation of Informed Consent**
- 5.5 Subjects who are Unable to Read**
- 5.6 Non-English Speaking Subjects**
- 5.7 When a Legal Representative is Required**
- 5.8 Consent For Research In Emergency Situations**
- 5.9 Consent on the Removal or Use of Human Tissue or Health Information for Research in Deceased Persons**
- 5.10 Waiver of Documentation of Consent**
- 5.11 Waiver of Informed Consent**
- 5.12 Special Requirements in Consent Taking for Restricted HBRA Regulated Research**

## **5.1 Important Considerations for the Informed Consent Process**

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The DSRB requires that informed consent must be obtained from all human subjects prior to their participation in any research unless the process, or any part thereof, has been waived by the DSRB.

Informed consent is the process by which a subject voluntarily confirms his or her willingness to participate in a particular research project, after having been informed of all aspects of the research study that are relevant to his or her decision to participate. Informed consent is to be documented by means of a written, signed, and dated ICF.

The informed consent process is necessary to ensure that subjects are fully informed before deciding whether to volunteer in research studies of any type. The PI should also ascertain to the best of his / her ability that any persons making a decision on behalf of the subject, acts in the best interest of the subject and had regard, to the subject's past and present wishes and feelings and any factors which the subject would consider if he / she were able to do so.

The most current version of the ICF approved by the IRB and regulatory authority (if applicable) should be used as a guide while describing to the subjects all the necessary information that they need to make an informed decision about participating in the study.

The following considerations should be kept in mind while conducting an informed consent discussion. Any exceptions must be specifically addressed and approved by the DSRB prior to implementation.

- a. Subjects must be given adequate time to consider and ask questions before making a decision whether or not to participate. For high risk studies, this might mean letting the subject bring home the consent form and return the next day or after a few days if the subject wishes to participate.
- b. Subjects should be encouraged to discuss participation in research with their family members.
- c. Subjects should be approached in an environment conducive for consent discussion. For example, it would not be appropriate to approach a subject immediately before a procedure or surgery, while in labour, while under sedation and in any other situation where a subject might feel compromised.
- d. Informed consent should be conducted by the PI, or a qualified member of the study staff who is listed in the DSRB Application Form as the designated person(s) /study role (s) for conducting the informed consent discussion. Any change to the designated person / study role for obtaining consent should be submitted to the DSRB for review and approval. The PI must ensure that the delegated person is appropriately trained to explain the benefits and risks of the study adequately and conduct the consent process appropriately without compromising on the quality of the consent.
- e. For clinical trials that are regulated by HSA, only the PI or an investigator authorized by the PI, who is a qualified practitioner is allowed to obtain informed consent from the subjects. Where the clinical trial is led by a pharmacist PI, co-investigators who are

qualified pharmacist may also be authorized by the PI to obtain consent. Individuals who are not qualified practitioners or qualified pharmacists are not allowed to obtain consent, but may assist in the consent process for such studies.

- f. Informed consent discussion should take place in person. Where it is not practicable for the researcher to obtain consent through a physical face-to-face interaction with the research subject, the researcher may consider obtaining consent remotely, including telephone calls, email correspondence and e-Consent.

*For more information on e-Consent, researchers may wish to access the **Guidance Document on Electronic Informed Consent Process** at <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOP & Templates.*

- g. Informed consent should be obtained before initiation of the study i.e. before any procedures that are being performed solely for the research.
- h. If the subject is unable to give informed consent, the informed consent discussion should be conducted with the subject's legal representative.
- i. The informed consent discussion must be conducted in a language understandable by the subject.
- j. Should a witness be required during the consent process, the study team member who conducted the informed consent discussion must inform the witness of their responsibilities of taking reasonable steps to ascertain:
  - i. The identity of the individual giving the appropriate consent;
  - ii. That the consent was given voluntarily without any coercion or intimidation.
- k. The informed consent process is not a one-time event carried out prior to enrolling research subjects, but must be a continuous ongoing process. Investigators must inform subjects of any important new information that may affect their willingness to continue participation in the study. The DSRB must approve the methods and materials for participant notification prior to implementation. Such methods may include (but are not limited to):
  - i. Information Letter,
  - ii. Addendum to previously signed consent form to be signed by subject, or
  - iii. Revised consent form to be signed by subject.
- l. Fresh consent from the subject would be required if existing personal data collected is to be used for a different purpose after July 2014. The DSRB approval on the revised ICF will need to be obtained prior to that re-consenting.
- m. Informed consent should include information on who the subject can contact for more information on the study or to voice their concerns or complaints. The PI is responsible for

addressing the subject's concerns/ complaints. The PI may refer the subject to the DSRB if the subject is not satisfied with the PI's response to the concerns/ complaints.

### **5.1.1 Additional Witness Requirements (For HBRA regulated studies)**

For studies regulated by the HBRA, appropriate consent must be taken in the presence of a prescribed witness:

- a. Who is 21 years of age or older;
- b. Who has mental capacity;
- c. Who must not be the same individual taking the appropriate consent; and
- d. Who may be a member of the team carrying out the research.

If the subject is unable to read or personally sign and date on the ICF, the witness should be an impartial witness (i.e. not be a member of the study team).

### **Exemptions for requiring a Prescribed Witness**

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

- a. Is not invasive;
- b. Is not interventional; and
- c. Is not restricted human biomedical research.

For example, human biomedical research that comprises solely of a survey or collection of information from subjects may be treated as not invasive and not interventional\*, subject to the determination of the DSRB, thus they may be exempted from the requirements for witness.

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

- a. The research is interventional but the intervention involves no more than minimal risk to the research subject;
- b. The research subject is able to read and sign the appropriate consent form; and
- c. The research is not a restricted human biomedical research.

\**Interventional: The HBRA defines research as interventional if it involves any activities that have physical, mental or physiological effect (whether temporary or permanent) on the body of the research subject. Examples of intervention include (but are not limited to) buccal swabs, drawing of blood for research purposes, X-ray or MRI scans. A research is not considered interventional (nor invasive) if the intervention is carried out primarily for non-research purposes (i.e. routine clinical procedure).*

### **5.1.2 Withdrawal from Research**

When the subjects withdraw from a research, the discussion between the investigator and the subject should distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

- a. An investigator may ask a subject who is withdrawing, whether the subject wishes to allow continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study.
- b. If a participant withdraws from the interventional portion of a study and consents to allow continued follow-up and further data collection, the investigator must obtain the subject's consent for this limited participation.

The DSRB must approve the consent document for the limited participation if such a situation was not described in the original consent document.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for the purposes related to the study the subject's medical records or other confidential records requiring subject's consent. However, an investigator may review study data related to the subject, collected prior to the subject's withdrawal from the study, and may consult public records such as those establishing survival status.

## **5.2 Developing the Informed Consent Form (ICF)**

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### **5.2.1 Required Elements of Informed Consent**

The following elements must be present in the consent form:

- a. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- b. A description of any reasonably foreseeable risks or discomforts to the subject.
- c. A description of any benefits to the subject or to others that may reasonably be expected from the research.
- d. A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.
- e. A statement describing the extent to which, if any, confidentiality of records identifying the subject will be maintained and that notes the possibility that the regulatory authorities, IRB, and sponsor's monitors may inspect the records.

- f. An explanation as to whether any compensation is provided and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- g. An explanation of whom to contact to discuss problems and questions, obtain information and offer input to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject, and whom to contact in the event of complaints or feedback about research.
- h. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time, unless the immediate discontinuation will result in a risk of harm to the subject, without penalty or loss of benefits to which the subject is otherwise entitled.

### **5.2.2 Additional Elements of Informed Consent**

When appropriate, one or more of the following elements of information shall also be provided to each subject:

- a. The approximate number of subjects involved in the study.
- b. Possibility of randomisation to placebo, study, or comparator arms.
- c. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or foetus if the subject is or may become pregnant), which are currently unforeseeable.
- d. Anticipated pro-rated payment, if any, for reimbursement of travel, meal or other expenses incurred due to participation in the research.
- e. Any additional costs to the subject that may result from participation in the research (HBRA requirement).
- f. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- g. Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent.
- h. A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
- i. Whether the subject would wish to be re-identified in the case of an incidental finding<sup>^</sup> if the proposed research, or for tissue donors - the future research, expressly provides for such re-identification (HBRA requirement).

*<sup>^</sup>Incidental finding (IF) is a finding about a research subject that has potential health or reproductive importance to the research subject and is discovered in the course of conducting research but is unrelated to the purposes, objectives or variables to the study.*

- j. A statement that any data that have been collected until the point of withdrawal will be kept and analysed to enable a complete and comprehensive evaluation of the study (HBRA requirement).

- k. Whether individually-identifiable information obtained from the subject will be used for future research (HBRA requirement).
- l. Where applicable, whether biological material taken from the research subject will be destroyed, discarded or stored for future research (HBRA requirement).
- m. Whether the participation of the subject involves information or tissue in individually-identifiable form (HBRA requirement).
- n. The circumstances, if any, under which, the research subject or the person authorised to give consent under this Part will be contacted for further consent, including but not limited to changes in the proposed research, the development of capacity by minors to make decisions and any other circumstances which could be specific to a particular research proposal (HBRA requirement).
- o. A statement that any biological specimen(s) collected as part of the research will not be returned to the subject as the subject has consented to gift it for the purpose of the research study and have given up his / her rights to it. However, the subject shall be allowed to request for his / her biological specimen(s) to be discarded or destroyed (e.g. upon withdrawal) if the biological specimen(s) is individually-identifiable and has not been used for the research or it has been used for research but it is practicable to discontinue further use of the biological specimen(s) for the research.
- p. When the research involves tests such as HIV testing, that require mandatory reporting to the Ministry of Health if positive, this should be disclosed in the informed consent form, as amended / updated in the MOH mandatory reporting policy.
- q. If the research involves genetic testing or DNA banking, the applicable issues in DNA banking and genetic research should be included.
- r. If the research involves establishing a specimen / tissue repository, the applicable issues in specimen collection for tissue / specimen repositories should be included.
- s. A statement of the intended research use of personal data, including whether biological specimen with personal data could be sent out of Singapore to an overseas collaborator.
- t. Any other information that is, in the DSRB's judgment would add meaningfully to the protection of the rights and welfare of subjects.

**For clinical trials regulated by Health Sciences Authority (HSA) involving the collection of human tissue (as defined by HSA)**

In addition to the elements listed in sections 5.2.1 and 5.2.2, the following elements must be present in the informed consent form:

- a) The provision of the tissue is voluntary and the renunciation of the trial participant's rights to use the tissue and any intellectual property rights that may be derived from the tissue;
- b) Whether the trial participant would wish to be re-identified in the case of an incidental finding<sup>^</sup> relating to the collected tissue if the research expressly provides for such re-identification;

- c) Whether the tissue will be exported or removed from Singapore to a place outside Singapore.

**For studies involving tissue banking activities (e.g. removal, donation, supply or use of human tissue as defined by HBRA) regulated under the HBRA Human Tissue Framework**

Examples of tissue banking activities may include, but are not limited to:

- a) Collection of left over tissue from a current HBR or clinical trial for future research;
- b) Collection of tissue beyond the objectives and endpoints of the protocol approved by the IRB and/or regulatory agencies e.g. HSA;
- c) Collection of additional tissue beyond what is approved in the current HBR or clinical trial;
- d) Supply of leftover tissue from a researcher's own HBR or clinical trial to other researcher(s) for research that is not the researcher's own IRB-approved research,
- e) Use of tissue for pre-clinical studies (e.g. research conducted using human tissue before actual clinical trial starts).

In addition to the elements listed in sections 5.2.1 and 5.2.2, the following elements must be present in the consent form:

- a. An explanation of the specific research purpose for which the tissue is intended to be used, if this information is available but if not available, the purpose for which the tissue is intended to be used may be stated as for general research.
- b. A statement to describe whether the tissue will be used for any purpose other than research and if so, the specific purpose for which the tissue will be used.
- c. A statement that the donation of the tissue is voluntary and the renunciation of the donor's rights to the tissue and any intellectual property rights that may be derived from the use of the tissue.
- d. A description of the proposed area(s) of research approved by the IRB in a case where it has waived the requirement that the removal of the tissue is primarily for a therapeutic or diagnostic purpose.
- e. A statement about whether the tissue will be used in restricted human biomedical research involving human-animal combinations.
- f. Whether the tissue will be exported or removed from Singapore to a place outside Singapore.

*<sup>^</sup>Incidental finding (IF) is a finding about a research subject that has potential health or reproductive importance to the research subject and is discovered in the course of conducting research but is unrelated to the purposes, objectives or variables to the study.*

NHG researchers may access the NHG Incidental Findings Policy at <https://mynhg.nhg.com.sg> > Home > Group Research > Research Compliance Unit.

### 5.2.3 General Considerations for the ICF

Whether using the sponsor generated consent form or developing a consent form for an investigator initiated study, the PI must ensure that the following aspects should be considered when drafting ICFs:

- a. All the required elements, as outlined above, are present in the consent form.
- b. SECOND PERSON - The language of the ICF should be written in second person style so that the consent form conveys information in dialogue form, which presents the subject with a choice for participation in the research study. Use of a first person persona for the consent document should be avoided; as such a format is presumptive of the subject having given consent for participation.
- c. SIMPLICITY – The information provided in the ICF must be in a language understandable to the subject. The ICF should not include complex language that would not be understandable to the subjects. Technical and scientific terms should be adequately explained using common or lay terminology.
- d. EXONERATORY LANGUAGE – The ICF may not contain any exoneratory language through which the subject is made to waive, or appear to waive legal rights, or releases or appears to release the investigator, the sponsor, or the institution from liability for negligence.
- e. FDA-REGULATED TEST ARTICLES – For all research involving test articles regulated by the US FDA, the ICF must include a statement that the purpose of the study includes evaluation of both the safety and effectiveness of the test article. The consent document must also include a statement that the FDA will be given access to the subject's medical records.
- f. DOCUMENT FOOTER AND PAGE NUMBER – The version number and version date of the ICF should be clearly stated as document footer at the bottom of every page. The page number (i.e. Page X of Y) should also be clearly stated at the bottom of every page.

The PI may use the NHG DSRB Informed Consent Form (ICF) Template to develop the consent form. For the most current version of the template, refer to NHG Research Website (<https://www.research.nhg.com.sg>) > Resources > Ethics Forms and Templates.

## **5.3 Study Team Members Authorised to Take Consent**

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Informed consent discussion should be conducted by the PI or a qualified member of the study team who is listed in the DSRB application form as the designated person / study role for conducting the informed consent discussion. The study responsibility log should also indicate all study staff delegated by the PI to take informed consent. Any change to the designated person(s) or study team role(s) delegated to take consent should be submitted to the DSRB for review and approval. The PI must ensure that the delegated person is appropriately trained to explain the benefits and risks of the study adequately and conduct the consent process appropriately without compromising on the quality of the consent.

### **5.3.1 Consent for HSA Regulated Clinical Trials**

For HSA-regulated clinical trials, only the PI or an investigator authorized by the PI, who is a qualified practitioner, is allowed to obtain informed consent from the subjects. Where the clinical trial is led by a pharmacist PI, co-investigators who are qualified pharmacists may also be authorized by the PI to obtain consent. Individuals who are not qualified practitioners or qualified pharmacists are not allowed to obtain consent, but may be delegated to assist in the consent process for such studies.

**QUALIFIED PRACTITIONER** – Under the Health Products Act (Clinical Trials) and Medicines (Clinical Trials) Regulations, this refers to:

- a. A registered medical practitioner under the Medical Registration Act (Cap. 174); or
- b. A registered dentist under the Dental Registration Act (Cap. 76) whose name appears in the first division of the Register of Dentists maintained and kept under section 13(1)(a) of that Act.

**QUALIFIED PHARMACIST** – Under the Health Products (Clinical Trial) Regulations, refers to an individual who:

- a. Is a registered pharmacist under the Pharmacists Registration Act (Cap. 230);
- b. Holds a valid practicing certificate granted under section 23 of that Act; and
- c. Is in active practice as defined in regulations 2 of the Pharmacist Registration (Practicing Certificate) Regulations 2008 (G.N.No.S 438/2008).

## **5.4 Documentation of Informed Consent**

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### **5.4.1 General Requirements for Consent Documentation**

In most circumstances, the DSRB will require that informed consent is documented by the use of a written consent form approved by the DSRB and signed by the subject or the subject's legal representative.

Each subject or his / her legal representative must personally sign and date a copy of the most current DSRB-approved ICF prior to enrolment or participation in any aspect of the study, unless this requirement has been waived by the DSRB. The subject or his / her legal representative must be given a complete copy of the signed ICF. A complete copy of the original signed ICF should also be filed in the investigator file.

The DSRB may approve procedures for documentation of informed consent that involve any of the three options listed below. The DSRB will determine which procedure is appropriate for the research study being reviewed:

- a. A written ICF signed by the subject or legal representative; or
- b. A written ICF appended with a short consent form, with oral presentation; or
- c. In limited circumstances, a waiver of the signed written ICF.

The study team member who conducted the informed consent discussion must personally sign and date the ICF. Additionally, the study team member who obtained the subject's consent must minimally record the following in the subject's source documents (e.g. medical records, if applicable).

- a. Protocol reference (e.g. protocol number, protocol title);
- b. Date of informed consent;
- c. Informed consent process (e.g. for use of substituted consent / impartial witness / prescribed witness (per Section 5.1.1), translator, verification of the appropriate legal representative for consent, use of assent form)
- d. Whether a copy of the signed ICF was given to the subject.

Documentation in the medical records is not required if the study does not involve access to medical records such as survey study, or observational epidemiological study. However, minimally required information on the informed consent process should be documented in other source documents.

Where applicable, reasonable efforts must be made to contact legal representatives in the descending order of priority in accordance to applicable regulations, and such efforts and reasons of unavailability (e.g. overseas, deceased) of prior class must be documented.

As per institutional requirements, a copy of the ICF may need to be filed in the medical records, to document the subject's participation in a research study. If the ICF is not placed in the

medical records due to confidentiality reasons, a statement in the medical records indicating the subject's participation in the research study should be included. If the research protocol may impact the subject's health, a statement in the medical records must include enough description of the intervention for other healthcare professionals to deal with any medical problems that may arise.

When participation in the study might impact the subject's health and / or medical care, the attending or referring doctor should be informed of the subject's participation in the study, if the participant agrees for the attending or referring doctor to be informed.

In certain situations, the DSRB may approve a request for waiver or alteration to the informed consent process. More information on this is provided in chapter 5.10 Waiver of Documentation of Consent and chapter 5.11 Waiver of Informed Consent.

#### **5.4.2 Documentation of Informed Consent for Mentally Competent Subjects Who Are Incapable of Personally Signing and Dating the Consent Form**

Situations may be encountered in which mentally competent subjects are unable to personally sign and date the ICF. Examples may include:

- a. Subjects with physical disabilities that prevent them from being able to write;
- b. Subjects who are unable to read the ICF (e.g. illiterate or visual impairment).

It should be ascertained that these subjects demonstrate mental competence and are able to understand the informed consent discussion. Subjects should also be capable of indicating approval or disapproval to study entry, to qualify for enrolment.

Documentation of informed consent for these subjects should be performed in the following manner:

- a. The subject should affix his or her thumbprint onto the ICF;
- b. An impartial witness will be required to attend the consent discussion, as well as sign and date on the ICF;
- c. The impartial witness may also write the subject's name and the date of consent on the ICF, on the subject's behalf; and

The person taking consent should document and clearly describe the informed consent process in the subject's source documents (e.g. medical records).

### **5.5 Subjects who are Unable to Read**

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When a subject or his or her legal representative is unable to read (i.e. illiterate or unable to read due to visual impairment), an impartial witness should be present during the entire informed consent discussion. The impartial witness should not be a member of the study team. If a translator is being used, this person can serve as a witness. The person conducting the consent discussion should read and explain the consent form to the subject or the legal representative.

- a. The IRB approved ICF and any other written information to be provided to the subjects) should be read and explained to the subject or his or her legal representative.
- b. The subject or his or her legal representative must provide verbal consent to the subject's participation in the study.
- c. If capable of doing so, the subject or his / her legal representative should personally sign and date the ICF.
- d. The witness should also personally sign and date the ICF. By signing the ICF, the witness attests that:
  - i. the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or his or her legal representative; and
  - ii. the informed consent was freely given by the subject or his or her legal representative.
- e. After obtaining the witness signature, the study team member conducting the consent discussion should personally sign and date the ICF. The person conducting the consent discussion should give a complete copy of the signed ICF to the subject or his or her legal representative.

## **5.6 Non-English Speaking Subjects**

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### **5.6.1 Use of Translated ICFs**

The preferred method of taking consent from non-English speaking subjects (who are literate in another language) is to provide the subjects with the ICF written in the language understandable to them. It is not acceptable to exclude potential subjects based on their inability to speak and understand English.

If the study involves many non-English speaking subjects, the PI should include and project the costs for translations of the DSRB approved ICFs into the study grants and contract. It is the PI's responsibility to ensure that there is provision of adequate resources to obtain proper informed consent from subjects.

A certified translation of the DSRB approved ICF into the language understandable to the subject is preferred. The fully translated ICF should be accompanied by a letter of certification from the translator or translation service, and kept in the investigator file.

For investigator-initiated studies where the costs of translation is a factor of concern, a certified translation is not required; documents translated by an individual fluent in the given language are acceptable. However, a letter from the translator describing his or her qualifications to perform the translation should be provided with the translated documents and kept in the investigator file.

*To document the translation process by a qualified individual, the PI may use the NHG DSRB Certification of Translation template. This template is available for download at <https://www.research.nhg.com.sg> > Resources > [Ethics Forms & Templates](#).*

### **5.6.2 Use of the Short Consent Form**

In the event where the ICF has not been translated and is not available in a language understandable to the subject, an alternative for investigator-initiated studies (for all types of research), is to provide an oral presentation of informed consent information and documented using **both**:

- a. The DSRB approved English language ICF serving as the written summary of the information to be orally translated and presented to the subject; and
- b. A short consent form (in a language understandable to the subject) stating that the elements of informed consent have been presented orally to the subject or the subject's legal representative.

When the short consent form is used, the following requirements should be used:

- a. The oral presentation and the short consent form should be in a language understandable to the subject;
- b. An impartial witness is required during the informed consent process, and the impartial witness should be fluent in both English and the language understandable by the subject;
- c. The study team member who is obtaining consent may not be the witness to the consent;
- d. The subject or subject's legal representative, the study team member obtaining consent and the impartial witness must personally sign and date on both the DSRB approved English language ICF and the short consent form;
- e. The subject or subject's legal representative must be provided with a complete copy of the signed DSRB-approved English language ICF together with the short consent form.

The complete set of informed consent documents for non-English speaking subject is constituted by the following:

- a. The DSRB approved English language ICF; and
- b. The short consent form written in the language understandable by the subject.

The short consent form should be appended to the DSRB approved English language ICF as a single set of document. A document footer (mentioning the document version number and version date) and page number (i.e. Page X of Y) must be provided as a reference to link these two documents.

*The NHG DSRB Short Consent Form templates are available in three local languages (Mandarin, Malay and Tamil). These templates are available for download at <https://www.research.nhg.com.sg> > Resources > Ethics Forms & Templates.*

### **5.6.3 Additional Information**

Fully translated informed consent forms, and all language versions of the Short Consent Form appended to the English language informed consent form are not required to be submitted to the DSRB for acknowledgement/approval prior to the use of these documents

However, the PI:

- Should ensure the accuracy of the translations and ensure that correct versions of the translated documents are used.
- Should track all versions of the translated consent forms (i.e. fully translated or Short Consent Form) to be used in the investigator file.
- Is encouraged to use a log to track the translated study documents in the investigator file.

*Please refer to the NHG Research website <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOP & Template for a copy of the ICF Tracking Log and Study Document Translation Log.*

## **5.7 When a Legal Representative Is Required**

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**LEGAL REPRESENTATIVE** - Under the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations, this refers to a person who is authorised under the law and having capacity to consent on behalf of an individual (who is a subject or a prospective subject) to his / her participation in the clinical trial. A person who has such capacity is a person who does not lack capacity to so consent within the meaning of section 4 of the Mental Capacity Act.

**LEGALLY ACCEPTABLE REPRESENTATIVE** - Under the ICH GCP guidelines, this is defined as an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

**LEGALLY AUTHORISED REPRESENTATIVE** - Under DHHS regulations, this means an individual or judicial or other body authorised under applicable law to consent on behalf of a prospective to the subject's participation in the procedure(s) involved in the research.

For the purposes of research under the purview of DSRB, the terms legal representative, legally acceptable representative and legally authorised representative as defined above, are synonymous and may be used interchangeably.

A legal representative may give consent on behalf of the subject for participation in a research only when the individual is not capable of giving legally effective informed consent, such as in any of the following circumstances:

- a. A child as defined in Chapter 6.1;

- b. An individual who is cognitively impaired; or
- c. An individual who is unconscious.

*For the specific consent requirements in vulnerable populations, please refer to the following topics under Chapter 6:*

- *Chapter 6.1 Research Involving Children*
- *Chapter 6.2 Research Involving Pregnant Women, Foetuses and Neonates*
- *Chapter 6.3 Research Involving Cognitively Impaired Persons*
- *Chapter 6.4 Research Involving Prisoners*

## **5.8 Consent for Research in Emergency Situations**

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For research conducted in emergency situations, when prior consent of the subject is not possible, the consent of the subject's legal representative (if he / she is present) should be obtained.

Where prior consent of the subject is not possible, and where the subject's legal representative is not available within the window period in which the treatment must be administered, additional measures are required to protect the rights, safety and well-being of the subject being enrolled, as well as to ensure compliance with the applicable regulatory requirements.

### **5.8.1 HBRA Regulated Clinical Research Studies Conducted in Emergency Situations**

Under the HBRA, emergency research is deemed as human biomedical research where life-threatening emergency situations may arise such that appropriate consent may not be obtained before the research subject is subjected to any intervention, or after any individually-identifiable biological material is obtained from his or her body, or any of his or her individually-identifiable health information is used.

At the point of enrolment of each subject, provision is made for any person as follows (I) and (II) or combination of such persons,

- I. A medical practitioner who is registered under the Medical Registration Act (Cap.174) as a specialist in the specialty relating to the research and who is not involved in the research as a researcher or supervisor;
- II. A person approved by the Director by name, or holding the office or designation or falling within the description approved by the Director.

to certify to the best of that person's or combination of person's knowledge that the following listed below (a) and (e) have been complied with -

- a. The research subjects are in a life-threatening situation;

- b. There is no professionally accepted standard of treatment or the available treatments are unproven;
- c. The collection of valid scientific evidence is necessary to determine the safety and effectiveness of a particular intervention or treatment;
- d. Participation in the proposed research holds out the prospect of direct benefit to the research subject;
- e. Obtaining appropriate consent is not feasible because:
  - i. The subject will not have capacity within the time available to give their appropriate consent as a result of their medical condition or situation; and,
  - ii. The subject's legal representative is not available.

Following enrolment, the written certification for each subject should be retained on file for verification.

Provision must also be made for one of the following, whichever occurs first:

- a. The subject is to be informed as soon as is practicable after he or she regains capacity of his / her participation in the research and given an opportunity to withdraw from further participation in the research; or
- b. The subject's legal representative to be informed as soon as is practicable of the subject's participation in the research and to be given an opportunity to request that the subject be withdrawn from further participation in the research.

The PI should ensure that the subject or the participant's legal representative is informed about the research as soon as is practicable and must obtain informed consent for continued participation in the research.

Where the subject has been enrolled into a study, and where the subject or legal representative or any family member objects to the subject's continued participation in the study, the subject should be immediately discontinued.

### **5.8.2 Clinical Trials Conducted in Emergency Situations (regulated by the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations)**

Under the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations, a clinical trial in an emergency situation is deemed as a clinical trial which determines the safety or efficacy of the investigational product being tested in the trial on subjects where:

- a. The subjects are facing a life-threatening situation that necessitates intervention;
- b. The subjects are unable to consent to being subjects in the trial as a result of their medical condition; and

- c. It is not feasible to request consents from the legal representatives of the subjects within the window period.

**WINDOW PERIOD** – The time period after onset of the event, based on available scientific evidence, within which the investigational product must be used or administered to have its potential clinical effect.

## **I. Documentation Required Prior to Initiating the Clinical Trial**

Prior to initiating the study, the PI must provide the DSRB and HSA with documentation to indicate that this is a clinical trial of emergency situation. This documentation should be signed off by the PI who is a qualified practitioner and who is conducting the clinical trial, and 2 specialists in writing that:

- a. The clinical trial needs to be conducted on potential subjects who are facing a life-threatening situation, to determine the safety or efficacy of the investigational product;
- b. Available treatments or procedures are unproven or unsatisfactory;
- c. There is a reasonable prospect that participation in the clinical trial will directly benefit the potential subject because:
  - i. The potential subjects are facing a life-threatening situation that necessitates intervention;
  - ii. The appropriate non-clinical and clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the proposed use of the investigational product to provide a direct benefit to the potential subjects; and
  - iii. The risks associated with the clinical trial are reasonable in relation to what is known about:
    - A. The medical condition of the potential subject;
    - B. The risks and benefits of standard therapy, if any; and
    - C. The risks and benefits of the proposed use of the investigational product;
- d. The potential subjects are unable to consent to being subjects as a result of their medication condition;
- e. It is not feasible to obtain consent from the legal representative of the potential subjects within the window period;
- f. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical trial; and
- g. The clinical trial cannot be practicably carried out if prior consent from the subject or his legal representative must be obtained.

## **II. Documentation Required Prior to Enrolling Each Subject**

At the point of enrolment of each subject, an investigator of the trial who is a specialist and one specialist who is not conducting the trial must certify in writing before enrolling the subject in the trial that:

- a. The subject is facing a life-threatening situation which necessitates intervention;
- b. The subject is unable to give consent as a result of his or her medical condition;
- c. It is not feasible to obtain consent from the subject or to contact subject's legal representative within the window period in which the study treatment must be administered; and
- d. Neither the subject, nor his or her legal representative, nor any member of the subject's family, has informed any investigator of any objection to the subject's participation in the clinical trial.

The written certifications made prior to trial initiation and at the point of enrolment of each subject should be retained on file for verification.

## **III. Documentation Required After Enrolment of Each Subject**

If the consent of the subject in the clinical trial in an emergency situation cannot be obtained because of his or her medical condition, and it is not feasible to obtain consent from the legal representative of the subject within the window period; then the PI must ensure that, at the earliest feasible opportunity (including during the window period):

- a. All reasonable efforts are made to contact any member of the subject's family; and
- b. The member of the subject's family is given a full and reasonable explanation of the required elements in the informed consent; and
- c. The member of the subject's family does not object for the subject to be or continue being a subject in the trial.

Once the consent is obtained from the subject, the decision by the legal representative or family member ceases to apply. If the subject is unable to consent and consent is obtained from the legal representative, the decision by the family member ceases to apply.

Where the subject has been enrolled into a trial, and where the subject or legal representative or any family member objects to the subject's continued participation in the trial, the subject should be immediately discontinued.

## **5.9 Consent on the Removal or Use of Human Tissue or Health Information for Research in Deceased Persons**

When the prospective research subject or tissue donor is a deceased person, appropriate consent must be obtained:

- a. For the use of the deceased person's individually identifiable —
  - i. Biological material;
  - ii. Body or any part of the body; or
  - iii. Health information; or
- b. For the removal or use of human tissue for research from the deceased person, appropriate consent must be obtained from any of the following persons in the order of priority stated, when persons in prior classes are not available at the time of death, and in the absence of actual notice of contrary indications by the deceased person, or actual notice of opposition of a member of the same class or a prior class:
  - a. The spouse;
  - b. An adult son or daughter;
  - c. Either parent or a guardian of the deceased person at the time of the person's death;
  - d. An adult brother or sister;
  - e. The administrator or executor of the estate of the deceased person;
  - f. Any other person authorised or under obligation to dispose of the body of the deceased person.

## **5.10 Waiver of Documentation of Consent**

The DSRB may waive the requirement for the PI to obtain a signed ICF for some or all subjects if the DSRB finds that:

### **EITHER**

- a. All the following are true:
  - i. The only record linking the subject and the research would be the consent document;
  - ii. The principal risk would be potential harm resulting from a breach of confidentiality;
  - iii. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the participant's wishes will govern;

- iv. The research is not subject to FDA regulations.

OR

- b. All the following are true:
  - i. The research presents no more than minimal risk of harm to subject.
  - ii. The research involves no procedures for which written consent is normally required outside of the research context.

For FDA-regulated studies, the waiver of documentation of consent may be granted only if criteria (b) is met.

#### **5.10.1 Verbal and Implied Consent**

**Verbal Consent** - In cases where the documentation requirement is waived, the DSRB may require the PI to submit for review, a written description of the information that will be provided to the subject. This can be in the form of a written statement regarding the research, which involves the use of an information sheet that includes most or all of the elements of an ICF, but does not require the subject's signature. The PI must submit the written statement to DSRB for review and approval. The DSRB may require the Investigator to enquire with the subject if the investigator may record that subjects have given verbal consent in the study record (e.g. Enrollment log).

If providing a written statement is not feasible (for example, subject contact is made by phone only), the DSRB may ask to see a script of what will be said to prospective subjects to evaluate the consent process.

**Implied Consent** – DSRB may also approve for studies to use implied consent. For example, PI conducts a survey where the survey materials clearly state that by responding to the questions and returning the survey back, the recipients will be considered to have agreed to participate in the research. By sending back the completed survey, the recipient has implied that he or she consents to participate in the research study but has not signed on an informed consent document.

#### **5.10.2 Examples on Waiver of Documentation of Consent**

Examples of studies where a waiver of documentation of consent may be approved:

- a. When the identities of subjects will be completely anonymous and there is minimal risk involved in the study. The signed informed consent would be the only record linking the participant to the study, therefore it would be the only identifier in the study.
- b. A study in which the only document linking the subject to the research is the consent form, and the principal risk of harm is breach of confidentiality.
- c. When the study involves only a telephone interview.

The scenario given below illustrates how the criteria for a waiver of documentation of consent may be applied to a research study.

**Scenario:**

*A researcher plans to evaluate the effectiveness of a smoking cessation programme with women who are receiving prenatal care at the local health clinic. During a prenatal visit, any women who are already participating in the smoking cessation programme will be asked to complete a written questionnaire about the program. The one-time written questionnaire includes questions about how well the women are complying with the program and how they feel about their progress. There is no identifying information about the subjects on the questionnaire and whether the subjects complete the questionnaire has no effect on the care they may receive at the clinic.*

How the above example satisfies the criteria for waiver of documentation of consent:

- a. Minimal risk: The anonymous questionnaire fits the definition of minimal risk, and the only potential harm comes from the breach of confidentiality.
- b. Linkage: The consent document is the only record linking the subject and the research activity.
- c. Implied consent: By the virtue of completing the questionnaire, the subjects have consented to participate in the research.

**Acknowledgements**

- Institutional Review Board: Management and Function, 3<sup>rd</sup> edition, E. Bankert, B.G. Gordon, E. A. Hurley, S.P. Shirver (2022) Jones & Bartlett Learning Company: Chapter 6-5 Waiver of Documentation of Consent.

## **5.11 Waiver of Informed Consent**

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The DSRB may approve a consent procedure that alters or excludes some or all of the elements of informed consent, or waive the requirement to obtain informed consent, if the following are met:

- a. For studies which are regulated by the HBRA, and collecting individually-identifiable health information obtained or complied before 1 November 2017:
  - i. the research cannot reasonably be carried out without the use of the health information in an individually-identifiable form;
  - ii. the use of the individually-identifiable health information involves no more than minimal risk to the research subject;
  - iii. the waiver concerned will not otherwise adversely affect the rights and welfare of the research subject; and

- iv. 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.
- b. For studies which are regulated by the HBRA, and collecting individually-identifiable human biological material obtained before 1 November 2017:
  - i. the research cannot reasonably be carried out without the use of the human biological material in an individually-identifiable form;
  - ii. the use of the individually-identifiable human biological material involves no more than minimal risk to the research subject;
  - iii. the waiver concerned will not otherwise adversely affect the rights and welfare of the research subject; and
  - iv. 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/ her consent.
- c. For studies which are regulated by the HBRA, and collecting individually-identifiable health information or human biological material obtained or compiled on or after 1 November 2017;
  - i. the research cannot reasonably be carried out without the use of the human biological material or health information in an individually-identifiable form;
  - ii. the process of obtaining consent from the person, to which the individually-identifiable human biological material or health information relates, will involve a disproportionate amount of effort and resources relative to the research requirements;
  - iii. the use of the individually-identifiable human biological material or health information, as the case may be, involves no more than minimal risk to the research subject or donor;
  - iv. the waiver concerned will not otherwise adversely affect the rights and welfare of the research subject or donor; and
  - v. the human biomedical research or health information research would reasonably be considered to contribute to the greater public good.

Please refer to the Human Biomedical Research Act 2015 (Amendment of Third, Fourth and Fifth Schedules) Order 2017, Amendment of Fifth Schedule for more information.

- d. For all other studies which are not regulated by the HBRA:

- i. the research involves no more than minimal risk to the subjects;

- ii. the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- iii. whenever appropriate, the subjects will be provided with additional pertinent information after participation;
- iv. the research could not practicably be carried out without the waiver or alteration; and
- v. the research is not subject to FDA regulations.

### **5.11.2 Examples on Waiver of Consent**

#### **Scenario 1:**

*Investigators will review the medical records of all patients who have undergone abdominal surgery in the past two years and correlate the data with blood chemistry values kept by pathology. Researchers are collecting limited data that will be assigned a random code number and the link is known only to the researchers. Results of the research will not affect clinical care of the individuals, since they have left the hospital.*

How the above example satisfies the criteria for waiver of informed consent:

- a. Minimal risk: Evaluating non-sensitive data from patient records fits the definition of minimal risk.
- b. Will not adversely affect rights and welfare of subjects: Surgery and associated blood chemistry values are clinically indicated, and therefore would be taken regardless of the research. The study result would not affect any clinical decisions related to the individual's care.
- c. Whenever appropriate, subjects will be provided with additional pertinent information after participation: Not appropriate in this case, since results of research would have no effect on the subjects. There are no anticipated benefits to the subjects that would change what has already occurred.

#### **Scenario 2:**

*A researcher plans to review the medical records using the same procedures in the previous example. However in this research, the hypothesis is that there is a correlation between a particular drug intervention and development of neurology problems several years later.*

As with the previous example, the DSRB may find that a waiver of informed consent is appropriate for the same reasons (part a, b and c) as outlined in the example. However, there is one important difference.

#### **Providing Additional Pertinent Information**

In this example, the DSRB may determine that it would be appropriate to provide these subjects with additional information about the results of the study. For the DSRB to make this determination, the DSRB may require the researcher to submit the results of the research, along with an assessment of whether subjects should be provided additional pertinent information, to the DSRB for review. The DSRB may require the researcher to outline a process that would include how the information about the research results would be

communicated to the subjects, what the results might mean and what to do if there are any questions.

## Acknowledgements

- Institutional Review Board: Management and Function, R. Amdur and E. Bankert, Chap. 6-6, "Research without Consent or Documentation Thereof," M. M. Elliott.

## **5.12 Special Requirements in Consent Taking for Restricted HBRA Regulated Research**

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For restricted research, appropriate consent must be obtained from the research subject who has capacity to give consent in person, and must not be obtained from another person who is authorized under the subject's or donor's behalf.

### **5.12.1 Appropriate consent of the donor of oocyte or embryo**

The appropriate consent of the donor of any oocyte or embryo for the purpose of restricted research –

- a. Must be obtained from the donor in person and only if the donor has capacity to give consent; and
- b. Must not be obtained from another person who is authorised to give consent on the subject's behalf.

Every research institution and every PI must ensure that consent from the donor of any oocyte or embryo for the purpose of restricted research must be separately and independently obtained from any consent for assisted reproduction treatment or any other therapeutic purpose. So long as the consent from the donor of any oocyte or embryo for the purpose of restricted research is separately and independently obtained from any consent for assisted reproduction treatment or any other therapeutic purpose, the consent from the donor need not be taken on different days.

The potential donor of any oocyte must confirm in writing at the time that her consent is taken that she had been informed of the full implications of the donation and that she does not require her oocyte for future reproductive use.

The potential donor of any embryo and her husband at the time of the assisted reproduction treatment must both confirm in writing at the time that the consent is taken that:

- a. They have each been informed of the full implications of the donation; and
- b. They do not require the embryo for future reproductive use.

The research institution and the PI must ensure that:

- a. Only surplus embryos created in assisted reproduction treatment may be used for research; and
- b. The consent of both the potential donor of the surplus embryo and her husband at the time of that assisted reproduction treatment had been obtained.

The consent from the donor of any oocyte or embryo for the purpose of restricted research must be obtained only after a period of 8 days after the day all the relevant information necessary for the informed consent had been given to the donor.

# **CHAPTER 6**

# **RESEARCH IN VULNERABLE POPULATIONS**

- 6.1 Research Involving Children**
- 6.2 Research Involving Pregnant Women, Foetuses and Neonates**
- 6.3 Research Involving Cognitively Impaired Persons**
- 6.4 Research Involving Prisoners**

## **6.1 Research Involving Children**

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The DSRB regards children as a vulnerable population and requires additional protection to be in place when children are to be included in research.

### **6.1.1 Definitions**

**ASSENT** – A child's affirmative agreement to participate in research. Mere failure to object and absent affirmative agreement should not be construed as assent.

**CHILDREN** – Persons who have not attained legal age for consent to treatments or procedures involved in the research (i.e. minors), which under Singapore law is an individual under the age of 21 years. However, persons who are below the age of 21 but are or were married are considered as adults who can give legally effective consent.

**DEPUTY** – An individual appointed by the court under the Mental Capacity Act who is given the authority to make decisions on behalf of a person who lacks capacity.

**GUARDIAN** – An individual who is authorised under law to give permission on behalf of the child to general medical care.

**LEGAL REPRESENTATIVE** – Under the Health Products (Clinical Trials) and Medicines (Clinical Trials) Regulations, where the subject or prospective subject is a minor, the legal representative refers to:

- a. A deputy appointed under the Mental Capacity Act in relation to the giving or refusing of consent on behalf of a minor to being a subject in clinical trials; or
- b. If there is no deputy referred to in (a), an adult parent, or (if there is no adult parent to act as a legal representative of the minor) a guardian, of the minor.

**PARENT** – The child's biological or adoptive parent.

**PERMISSION** – The agreement of the parent(s) or guardian to the participation of their child or ward in research.

**WARD** – A child who is placed in the legal custody of the court or other agency, institution, or entity.

### **6.1.2 Categories of Research for Studies Involving Children**

Children can be included in research only if the research fulfils any of the following three categories:

**CATEGORY 1** – Research that does not involve more than minimal risk. In order to approve research in this category, the DSRB must determine that adequate provisions are made for

soliciting the consent/ assent of the children and the consent of their parents or guardians (or the legal representative as stipulated in the applicable regulations if different).

**CATEGORY 2** – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. In order to approve research in this category, the DSRB must determine that:

- a. The risk is justified by the anticipated benefit to the subject;
- b. The relation of the anticipated benefit to the risk is at least as favorable to the subject as that presented by alternative approaches; and
- c. Adequate provisions are made for soliciting the consent/ assent of the children and the consent of their parents or guardians (or the legal representative as stipulated in the applicable regulations if different).

**CATEGORY 3** – Research involving greater than minimal risk and no prospect of benefit to the individual subjects. In order to approve research in this category, the DSRB must determine that:

- i. The risk of the research presents no more than a minor increase over minimal risk;
- ii. The intervention or procedure presents experiences to the subject that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations, and;
- iii. The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or the amelioration of the disorder or condition; and
- iv. Adequate provisions are made for soliciting the consent / assent of the children and the consent of their parents or guardians (or the legal representative as stipulated in the applicable regulations if different).

Reasonable prospect of direct benefit to a person means:

- a. Appropriate non-clinical and clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the proposed use of the investigational product to provide a direct benefit to the person; and
- b. The risks associated with the trial are reasonable in relation to what is known about:
  - i. The medical condition of the person;
  - ii. The risks and benefits of standard therapy, if any;
  - iii. The risks and benefits of the proposed use of the investigational product.

### **6.1.3 Consent Requirements for Studies Involving Children**

PARENTAL PERMISSION – Since children have not reached their full intellectual and emotional capacities and are legally unable to give a valid informed consent, involving children in research requires the permission of their parents or legal guardian. The DSRB will use the following guidelines to determine consent / assent requirements:

- a. If both parents are available and willing to provide permission, the PI should obtain consent from both parents.
- b. For research approved under Category 1 and 2, permission from at least one parent or guardian must be obtained.
- c. For research approved under Category 3, permission must be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

### **I. Clinical Research Studies Regulated under the HBRA**

Human biomedical research studies involving children are subject to the requirements laid out in the HBRA. Appropriate consent must be obtained from the following persons in the following circumstances:

- a. Where the minor has sufficient understanding and intelligence to enable the minor to understand what is proposed in the biomedical research, consent is obtained from both the minor and at least one adult parent or guardian of the minor;
- b. Where the minor has sufficient understanding and intelligence to enable the minor to understand biomedical research and the DSRB has waived the requirement to obtain the consent of at least one adult parent or guardian of the minor, consent is obtained from the minor;
- c. Where the minor does not have sufficient understanding and intelligence to enable the minor to understand what is proposed in the research and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of minors to which the minor belongs, consent is obtained from at least one parent or guardian of the minor;
- d. Where the minor lacks mental capacity and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of minors to which the minor belongs, consent is obtained from:
  - i. Deputy who is authorised to give consent to the biomedical research on behalf of the minor; or
  - ii. At least one adult parent or guardian of the minor.

### **Ia. Consent for removal or use of tissue for research from minors**

Where the prospective tissue donor is a minor, the appropriate consent for the removal or use of human tissue must be obtained from the following persons in the following circumstances:

- a. where the minor has sufficient understanding and intelligence to enable the minor to understand what is proposed in the procedure, consent is obtained from both the minor and at least one adult parent or guardian of the minor;
- b. where the minor does not have sufficient understanding and intelligence to enable the minor to understand what is proposed in the procedure and the removal of the tissue is primarily for a therapeutic or diagnostic purpose, consent is obtained from at least one adult parent or guardian of the minor;
- c. where the minor lacks mental capacity and the removal of tissue is primarily for a therapeutic or diagnostic purpose, consent is obtained from:
  - i. A deputy who is authorised to give consent for the removal or use of the tissue on behalf of the minor; or
  - ii. At least one adult parent or guardian of the minor.

For the purpose of consent for the removal or use of tissue for research from minors, the deputy, adult parent or guardian of a minor must, in determining whether to give consent under that the above mentioned circumstances, have regard to such matters, considerations and procedures as may be prescribed.

The DSRB may waive the requirement that the tissue be removed from a minor primarily for a therapeutic or diagnostic purpose if the board is satisfied that:

- a. the removal of the tissue involves no more than minimal risks to the minor; and
- b. there are reasonable grounds for believing that the proposed areas of research cannot be carried out without the use of the tissue from that class of persons, i.e. minors.

### **II. Clinical Trials**

Clinical trials involving children are subject to the requirements laid out in the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations.

The DSRB must ascertain that the following conditions are met:

- a. The child and / or the child's legal representative will be given a full and reasonable explanation of all the required elements of the informed consent; and
- b. The child and / or the child's legal representative consent will be obtained.

The investigator, who must be a qualified practitioner shall obtain the consent of the child as follows:

- a. In the case of a child below the age of 21 years who is or was married, the consent should be obtained from that child;
- b. In the case of a child below the age of 21 years who is not and was never married (i.e. minor), the consent of the child and:
  - i. The consent of the child's legal representative; and
  - ii. If that legal representative is below 21 years of age, the legal representative must have sufficient understanding and intelligence to give the consent.
- c. In the case of a child below the age of 21 years of age who is not and was never married (i.e. minor), but who lacks capacity to give consent to being a subject, or the child lacks sufficient understanding and intelligence to give such consent, then the consent of the child need not be obtained if:
  - i. The child's legal representative consents to the child being a subject, and if the legal representative is below 21 years of age, has sufficient understanding and intelligence to give the consent; and
  - ii. There is a reasonable prospect that participation in the clinical trial will directly benefit that child.

#### **IIa. Non-therapeutic clinical trials involving children / minors**

For non-therapeutic clinical trials involving children/minors (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), the DSRB will ascertain that the following conditions are fulfilled:

- a. The objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;
- b. The trial is conducted in subjects having a disease or condition for which the investigational product being tested in the trial is intended;
- c. There is some direct benefit for the group of subjects involved in the trial;
- d. The foreseeable risks to the subjects involved in the trial are low;
- e. The negative impact on the wellbeing of subjects involved in the trial is minimised and low.

The PI should determine if the legal representative of the child (if below 21 years of age) has sufficient understanding and intelligence to give informed consent. If the child subsequently

regains capacity to consent to being a subject, the PI must ensure that, at the earliest feasible opportunity:

- a. The child is given a full and reasonable explanation of the required elements of the informed consent; and
- b. The child's consent to continue being a subject in the trial is obtained.

If the child refuses to consent, the PI must ensure that the child ceases to be a subject in the clinical trial.

Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

### **III. Other Research Studies**

For other research studies not regulated under the Health Products (Clinical Trials) Regulations, Medicines (Clinical Trials) Regulations or the HBRA, and where the prospective research subject is a minor, the investigator should obtain consent from at least one adult parent or guardian of the minor. In the Singapore context,

- a. When the parents are divorced, the parent who has legal custody has sole legal responsibility for the care and custody of the child. Therefore under DHHS and FDA regulations only the permission of the parent who has legal custody is required. The parent who has legal custody is the legally acceptable representative for the child.
- b. When the child is illegitimate, the mother has sole legal responsibility for the care and custody of the child. Therefore under the DHHS and FDA regulations only the permission of the mother is required. The mother is the legally acceptable representative for the child.
- c. The following individuals are legally acceptable representatives and meet the DHHS and FDA definitions of "guardian" as they have the same rights as a parent to consent on behalf of the child to general medical care:
  - i. A guardian appointed under the Guardianship of Infants Act.
  - ii. A person to whom the care of a child is committed under the Children and Young Persons Act.

The PI should ascertain to the best of his ability that any persons making a decision on behalf of the subject, acts in the best interest of the subject and has regard, to the subject's past and present wishes and feelings and any factors which the subject would consider if he were able to do so.

#### **6.1.4 Waiver of Consent from Parents / Guardians**

Consent from parents / guardians may not be appropriate in cases such as in research involving child abuse or neglect. The DSRB will follow the respective criteria when reviewing requests for the waiver of consent from the child's parent / guardian.

#### **I. Clinical Research Studies Regulated under the HBRA**

For human biomedical research studies regulated under the HBRA, the DSRB may consider a waiver of consent of at least one adult parent or guardian if the research study meets the following criteria:

- a. The proposed research involves no more than minimal risk to the research subjects;
- b. The waiver of parental consent will not adversely affect the rights and welfare of the research subjects; and
- c. The proposed research may not practicably be carried out unless there is such a waiver, and the research proposal:
  - i. Is designed for conditions or for a research subject population for which parental or guardian consent is not a reasonable requirement to protect the research subject (such as neglected or abused minors), and an appropriate mechanism for protecting the minors is substituted; or
  - ii. Is of such private and sensitive nature that it is not reasonable to require permission, (such as adolescents in studies concerning treatment of sexually transmitted diseases).

#### **II. Clinical Trials**

Under the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations, the requirement for parental consent cannot be waived in clinical trials involving minors.

#### **III. Other Research Studies**

For other research studies, the DSRB may consider a waiver of consent from parental consent if the study meets all of the following criteria:

- a. The research is designed for conditions or for a subject population for which parental or guardian consent is not a reasonable requirement to protect the subject;
- b. An appropriate mechanism for protecting the children who will participate as subject in the research is substituted;
- c. The research is not US FDA-regulated.

For HIV / STD research that poses less than minimal risk to children, the DSRB may consider waiving consent from parent permission if the study meets both of the following criteria, in addition to the general waiver criteria set out above (e.g. HBRA consent waiver criteria):

- a. Potential subjects have attained the legal age for consent for sexual activity (i.e. 16 years old).
- b. The study is pertinent to children in this particular age group (i.e. 16 to 20 years old).

#### **6.1.5 Assent by the Child**

**ASSENT BY THE CHILD** – While a child may not have sufficient understanding and intelligence to understand what is proposed in the research, he/she may possess the ability to assent to or dissent from participation. Out of respect for children as developing persons, children who are unable to provide consent should be asked whether or not they wish to participate in the research particularly if the research does not involve interventions likely to be of benefit to the subject and the child can comprehend and appreciate what it means to be a volunteer for the benefit of others. Discussion with the child regarding the study and assent obtained (if applicable) should be documented.

In general, the DSRB requires that consent be obtained from children who are 12 years and above, if they have sufficient understanding and intelligence to do so, together with consent from their legal representative. For children who lack sufficient understanding and intelligence and who are 6 years and above, assent should be obtained, together with consent from their legal representative.

The DSRB will determine whether all or some of the children are capable of consent/ assent by considering the following:

- a. The nature of research;
- b. The age, status, condition of the proposed subjects; and
- c. Maturity and psychological state of proposed subjects.

As a general guide, children (who are 6 years and above) should be provided with a short assent document that clearly explains discomforts and inconveniences that the child may experience if he or she agrees to participate. The document should also emphasize the voluntary nature of the research and that the child may refuse to participate without any consequences. Where possible, the child should personally write his/ her name and date of assent in the assent form.

If the child is unable to personally write his/ her name and/or date on the assent form, the child could affix his/ her thumbprint (where possible). The impartial witness (i.e. not a member of the study team) should complete the child's name and/or assent date, personally sign and date on the assent form and an explanation should be documented in the source document

(e.g. assent form, medical records). A completed copy of the assent form should also be provided to the child/ legal representative.

For research involving children who are 12 years old and above and who have sufficient intelligence and understanding to provide consent, provision should be made in the same consent document that will be signed by the parents/ legal representative for the signature of the child. An explanation should be documented in the source documents if they are unable to provide consent.

It is recommended that where possible, PIs and study team should engage an independent assessor to determine whether the child (aged 12 years old and above) has sufficient understanding and intelligence to provide consent.

The DSRB must review and approve both the assent and consent document prior to initiation of the study.

The PI may use the NHG DSRB Assent Document Template to develop the child assent form.

*The NHG DSRB Assent Document Template is available for download at <https://www.research.nhg.com.sg> > Resources > [Ethics Forms & Templates](#).*

**WAIVER OF CONSENT / ASSENT BY THE CHILD** - The DSRB may determine that the consent / assent of the child is not necessary (unless prohibited by the applicable regulations) when either of the following are met:

- a. The children are not capable of providing consent / assent based on the age, maturity, or psychological state;
- b. The capability of the children is so limited that they cannot reasonably be consulted;
- c. The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research;
- d. The research meets the criteria for waiver of the consent process as set out in chapter 5.11 Waiver of Informed Consent, even when the children are capable of consent / assenting.

#### **6.1.6 Special Circumstances – Wards of Court**

Additional protections need to be in place when a Category 3 research (i.e. greater than minimal risk to the subject with no prospect of direct benefit to the individual subject) involves children who are wards of court or any other institution or entity. In order to approve such studies, the DSRB must determine that the research is:

- a. Related to their status as wards,

- b. Conducted in schools, hospitals, institutions, or similar settings where majority of the children involved as subject are not wards.

For such research, the DSRB will require the appointment of an advocate in addition to any other individuals who are acting on behalf of the child as a guardian. The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the research. This individual must not be associated in any way (except in the role of advocate or member of the DSRB) with the research, investigator or the guardian organisation.

## **6.2 Research Involving Pregnant Women, Foetuses and Neonates**

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The DSRB regards pregnant women, human foetuses, neonates of uncertain viability, or nonviable neonates (i.e. neonates determined to be unable, after delivery, to survive to the point of independently maintaining heartbeat and respiration) as a vulnerable population and requires additional protections to be in place when pregnant women, human foetuses, neonates of uncertain viability, or nonviable neonates are included in research.

### **6.2.1 Definitions**

**DEAD FOETUS** - A foetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

**DELIVERY** - Complete separation of the foetus from the woman by expulsion or extraction or any other means.

**FOETUS** - Foetus means the product of conception from implantation until delivery.

**NEONATE** – Refers to newborn.

**NONVIALE NEONATE** – Refers to a neonate after delivery that, although living, is not viable

**PREGNANCY** - Encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

**VIABLE** - As it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

### **6.2.2 Conditions for Research Involving Pregnant Women and Foetuses**

Pregnant women and foetuses may be involved in research if all of the following conditions are met:

- a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and foetuses;
- b. The risk to the foetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the foetus; or, if there is no such prospect of benefit, the risk to the foetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
- c. Any risk is the least possible for achieving the objectives of the research;
- d. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the foetus, or no prospect of benefit for the woman nor the foetus when risk to the foetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, and her consent is obtained;
- e. If the research holds out the prospect of direct benefit solely to the foetus, then the consent of the pregnant woman and the father is obtained, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy had resulted from rape or incest;
- f. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the foetus or neonate;
- g. For children who are pregnant, their consent / assent and their parents' consent are obtained;
- h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy;
- j. Individuals engaged in the research will have no part in determining the viability of a neonate.

### **6.2.3 Conditions for Research Involving Neonates**

Neonates of uncertain viability and nonviable neonates may be involved in research only if all of the following conditions are met:

- a. Where scientifically appropriate, preclinical and clinical studies have been conducted and data is provided for assessing potential risks to neonates;
- b. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate;

- c. Individuals engaged in the research will have no part in determining the viability of a neonate.
- d. Additional requirements as prescribed below for neonates of uncertain viability and nonviable neonates have been met.

**NEONATES OF UNCERTAIN VIABILITY** – Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions are met:

- a. The DSRB determines that:
  - i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or
  - ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate from the research.
- b. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legal representative is obtained, except that the consent of the father or his legal representative need not be obtained if the pregnancy resulted from rape or incest.

**NONVIALE NEONATES** – After delivery, nonviable neonates may not be involved in research covered by this subpart unless all of the following additional conditions are met:

- a. Vital functions of the neonate will not be artificially maintained;
- b. The research will not terminate the heartbeat or respiration of the neonate;
- c. There will be no added risk to the neonate resulting from the research;
- d. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means;
- e. The legally effective informed consent of both parents of the neonate is obtained, except that the waiver and alteration provisions do not apply.
  - i. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy had resulted from rape or incest.

- ii. The consent of a legal representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

**VIABLE NEONATES** – A neonate that has been determined to be viable after delivery may be included in research only to the extent permitted by, and in accordance with, the requirements stated in chapter 6.1 Research Involving Children.

#### **6.2.4 Conditions for Research Involving the Placenta, Dead Foetus or Foetal Material After Delivery**

Research involving (after delivery) the placenta, dead foetus, macerated fetal material, or cells / tissues / organs excised from a dead foetus, shall be conducted only in accordance with any regulations governing such activities.

Where information associated with the material described above is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those living individuals, those individuals will be considered as research subjects, and the conditions stated in chapter 6.2 Research involving Pregnant Women, Foetuses and Neonates (as described above and where applicable) will apply.

### **6.3 Research Involving Cognitively Impaired Persons**

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The DSRB regards cognitively impaired persons as a vulnerable population and requires additional protections to be in place when cognitively impaired persons are to be included in research.

#### **6.3.1 Definitions**

**COGNITIVELY IMPAIRED** – Having either a psychiatric disorder (e.g. psychosis, neurosis, personality or behaviour disorders), an organic impairment (e.g. dementia) or a developmental disorder (e.g. mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

**COMPETENCE** – A legal term used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Competence may fluctuate as a function of the natural course of a mental illness, response to training, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically.

**DEPUTY** – An individual appointed by the court under the Mental Capacity Act who is given the authority to make decisions on behalf of a person who lacks mental capacity.

**DONEE** – An individual appointed by a person under the Mental Capacity Act who is given the authority to make decisions on behalf of a person when he/she loses mental capacity.

**INCAPACITY** – Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence.

**INCOMPETENCE** – A legal term meaning the inability to manage one's own affairs. Often used as a synonym for incapacity.

**INSTITUTION** – A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long term care, and custodial or residential care).

**LEGAL REPRESENTATIVE** – Under the Health Products (Clinical Trials) and Medicines (Clinical Trials) Regulations, where the subject or prospective subject is an adult who lacks capacity to consent, the legal representative refers to -

- a. The donee or deputy appointed pursuant to or under the Mental Capacity Act in relation to the giving or refusing of consent on behalf of the adult to be a subject; or
- b. where there is no donee or deputy referred to in paragraph a., subject to paragraph c., any of the following persons in descending order of priority:
  - i. A spouse of the adult;
  - ii. An adult child of the adult;
  - iii. A parent or guardian of the adult;
  - iv. An adult sibling of the adult;
  - v. Any other adult named by the adult (when the adult did not lack capacity) as someone to consult on the issue of the adult being a subject.
- c. In addition, all of the following shall apply:
  - i. The order of priority applies in the absence of actual notice of any contrary indication given by the subject or prospective subject (when the subject or prospective subject did not lack capacity);
  - ii. A person referred to in paragraph (b) cannot be a legal representative of the subject or prospective subject if the person is also a donee or deputy and there is an express provision in the lasting power of attorney or appointment by the court that the donee or deputy is not authorised to give consent to the adult being a subject;
  - iii. A person referred to in paragraph b (ii), (iii), (iv) or (v):

- A. May be a legal representative only if all persons having a higher priority compared to that person are not available or cannot be a legal representative by reason of c (i) or (ii); and
- B. Cannot be a legal representative if any person having an equal or a higher priority compared to that person [other than a person who cannot be a legal representative by reason of c (i) or (ii)] has objected to the adult being a subject.

QUALIFIED PRACTITIONER – Under the Health Products (Clinical Trials) and Medicines (Clinical Trials) Regulations, the term Qualified Practitioner refers to an individual who is –

- a. A registered medical practitioner under the Medical Registration Act (Cap. 174); or
- b. A registered dentist under the Dental Registration Act (Cap. 76) whose name appears in the first division of the Register of Dentists maintained and kept under section 13(1)(a) of that Act.

### **6.3.2 Considerations for Research Involving Cognitively Impaired Persons**

As a general principle, incapable persons should not be involved in research that can be conducted with capable subjects. Inclusion of cognitively impaired persons may be permitted by HSA (for clinical trials) and DSRB if such research can provide access to an important benefit, particularly one that is not otherwise available outside of the research setting.

In addition to the general criteria for submitting research studies to the DSRB as described in chapter 4, the PI should consider the following points if the research involves cognitively impaired persons.

DEGREE OF RISK – Research that presents more than minimal risk should involve cognitively impaired persons only when the research holds prospects of direct benefit to these individuals. A minor increase over minimal risk may be permitted in research involving institutionalised individuals only where research is designed to evaluate an intervention of foreseeable benefit to their care. If a research study possesses more than minimal risk and no prospect of direct benefit to the individuals, the PI should justify to the DSRB the appropriateness of the research study.

Reasonable prospect of direct benefit to a person means:

- a. Appropriate non-clinical and clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the proposed use of the investigational product to provide a direct benefit to the person; and
- b. The risks associated with the trial are reasonable in relation to what is known about:
  - i. The medical condition of the person;
  - ii. The risks and benefits of standard therapy, if any;

iii. The risks and benefits of the proposed use of the investigational product.

**SELECTION OF SUBJECTS** – Research involving persons whose autonomy is compromised by disability or restraints on their personal freedom should bear some direct relationship to their condition or circumstances. Persons who are institutionalised should not be chosen for studies that bear no relation to their situation just because it would be convenient for the researcher.

**LIMITING RISKS** – Investigators should include a description of appropriate psychological or medical screening criteria to prevent or reduce adverse reactions to the therapeutic and research procedures. When appropriate, the DSRB might require other healthcare providers involved in the care of these patients to be consulted to ensure that the research will not be detrimental to on-going therapeutic regimens.

### **Assessing Competence**

As a general rule, all adults, regardless of their diagnosis or condition, should be presumed to be competent to consent unless there is evidence of a serious mental disability that would impair reasoning or judgment. Even those who do have a diagnosed mental disorder may be perfectly able to understand the matter of being a research volunteer, and quite capable of consenting to or refusing participation. Mental disability alone should not disqualify a person from consenting to participate in research; rather, there should be specific evidence of individuals' incapacity to understand and to make a choice before they are deemed unable to consent.

**DOCUMENTING CAPACITY** – For all research, regardless of study population, the person who obtains the subject's consent must determine that the person has sufficient capacity to give consent. This is documented by the signature in the ICF of the person obtaining consent. The investigator may use the NHG DSRB Sample Language for Documentation of Capacity template for this purpose.

In research that involves cognitively impaired persons, investigators should consider the need for an independent assessment of capacity. For participation in clinical trials, an independent assessment of capacity should be made by a doctor (who is a qualified medical practitioner). The DSRB may set qualifications for the person making assessment, such as requiring a psychiatrist or geriatrician to make this assessment. The independent assessment should be documented by a formal note that is dated and signed.

*The NHG DSRB Sample Language for Documentation of Capacity template is available for download at <https://www.research.nhg.com.sg> > Resources > [Ethics Forms & Templates](#).*

#### **6.3.3 Consent for Research Involving Cognitively Impaired Persons**

Informed consent is required for research studies involving cognitively impaired persons, unless waived under the conditions specified in chapter 5.11 Waiver of Informed Consent or under the following applicable criteria.

## **I. Clinical Trials (Regulated under the Health Products Act or Medicines Act)**

The consent of adults who lack capacity shall not be required if:

- a. The investigator who is a qualified practitioner, and another qualified practitioner who is a registered medical practitioner, who is not conducting the clinical trial certify in writing that –
  - i. The person lacks capacity to consent to being a subject; and
  - ii. It is not likely that the person will regain capacity within the window period;
- b. Consent has been obtained from –
  - i. That person's legal representative (as per the order of priority described in section 6.3.1); and
  - ii. If the legal representative is below 21 years of age, has sufficient understanding and intelligence to give the consent (the investigator should ascertain this); and
  - iii. It is established that there is a reasonable prospect that participation in the clinical trial will directly benefit that person.

### **Ia. Non-therapeutic clinical trials involving adults lacking capacity**

For non-therapeutic clinical trials involving adults lacking capacity (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), the DSRB will ascertain that the following conditions are fulfilled:

- a. the objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;
- b. the trial is conducted in subjects having a disease or condition for which the investigational product being tested in the trial is intended;
- c. there is some direct benefit for the group of subjects involved in the trial;
- d. the foreseeable risks to the subjects involved in the trial are low;
- e. the negative impact on the wellbeing of subjects involved in the trial is minimised and low.

If the adult subsequently regains capacity to consent to being a subject, the PI must ensure that, at the earliest feasible opportunity:

- a. The person is given a full and reasonable explanation of the required elements of the informed consent; and
- b. The person's consent to continue being a subject in the trial is obtained.

If the person refuses to consent, the PI must ensure that the person ceases to be a subject in the clinical trial.

Subjects in these trials should be particularly closely monitored and withdrawn if they appear to be unduly distressed.

## **II. Clinical Research Studies (Regulated under the HBRA)**

Where the prospective research subject is an adult who lacks mental capacity and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of persons to which the adult belongs, the appropriate consent for the adult must be obtained from the following persons in the following circumstances:

- a. Where there is a donee or deputy who is authorised to give consent to the biomedical research on behalf of the adult, consent is obtained from the donee or deputy;
- b. Where there is no donee or deputy who is authorised to give consent to the biomedical research on behalf of the adult, consent is obtained from any of the following persons in the order of priority stated, when persons in prior classes are not available, and in the absence of actual notice of contrary indications by the adult, or actual notice of opposition of a member of the same class or a prior class:
  - 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.

Where applicable, PIs must ensure reasonable efforts are made to contact legal representatives in the descending order of priority in accordance to applicable regulations, and such efforts and reasons of unavailability (e.g. overseas, deceased) of prior class must be documented.

### **IIa. Consent for removal or use of tissue for research involving adults who lack mental capacity**

Where the prospective tissue is from an adult who lacks mental capacity to consent to the removal or use of any human tissue, and the removal of human tissue from that adult is primarily for a therapeutic or diagnostic purpose, the appropriate consent must be obtained according to the HBRA requirements for Consent for research involving adults who lack mental capacity above.

If there is an express provision in the lasting power of attorney that the donee is not authorised to give consent to human biomedical research, the removal or use of tissue on behalf of the adult lacking mental capacity, that donee is not authorised to give consent.

### **III. Other Research Studies**

For other research studies not regulated under the Health Products (Clinical Trials) Regulations, Medicines (Clinical Trials) Regulations or the Human Biomedical Research Act, and where the prospective research subject is an adult who lacks capacity, the investigator should obtain consent from the following persons in descending order of priority:

- a. The spouse;
- b. The adult son or daughter;
- c. Either parent or a guardian;
- d. An adult brother or sister;
- e. Any other person named by the adult as someone to be consulted on the matter in question or on matters of that kind.

The DSRB may require the PI to obtain assent from prospective subjects' (i.e. the willingness and, to the extent possible, knowledge participation of those unable to give legally valid consent). The PI must obtain approval from DSRB for a simple assent form for use in such conditions.

For subjects who are unconscious and where it is not feasible to take consent from subjects or their legal representatives within the window period during which the research treatment must be administered, the consent requirements for clinical trials in emergency situations will apply.

*For more information please refer to chapter 5.8 Consent for Research in Emergency Situations.*

#### **6.3.4 Additional Consent Requirements**

The PI should ascertain to the best of his ability that any persons making a decision on behalf of the subject, acts in the best interest of the subject and has regard, to the subject's past and present wishes and feelings and any factors which the subjects would consider if he were able to do so.

The DSRB should consider whether to require investigators to solicit prospective subjects' assent (i.e., the willingness and, to the extent possible, knowledgeable participation of those unable to give legally valid consent).

Where appropriate, investigators must inform subjects of any important new information that may affect their willingness to continue participation. The DSRB must approve the method of notification prior to implementation. The method may include an information letter, an addendum to the previously signed ICF to be signed by subject or a revised ICF to be signed by the subject.

### **6.3.5 Incompetent Subjects who are Institutionalised**

**PERSONS WHO ARE INSTITUTIONALISED** – When the research poses more than minimal risk and has no prospect of direct benefit to the individuals:

- a. Persons formally adjudged incompetent who have a court appointed guardian may consent on their behalf.
- b. Officials of the institution in which incompetent patients reside (even if they are the patient's legal guardian) are not generally considered appropriate, since their supervisory duties may give rise to conflicting interests and loyalties.
- c. Family members or others financially responsible for patient may also be subject to conflicting interests because of financial pressures, emotional distancing, or other ambivalent feelings common in such circumstances.

## **6.4 Research Involving Prisoners**

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The DSRB regards prisoners as a vulnerable population and requires additional protections to be in place when prisoners are to be included in research.

**PRISONER** – An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution.

### **6.4.1 Considerations for Research Involving Prisoners**

Research involving prisoners should bear some direct relationship to their condition or circumstances. Prisoners should not be chosen for studies that bear no relation to their situation just because it would be convenient for the researchers. The two main issues surrounding the participation of prisoners in research are:

- a. Whether prisoners have a real choice regarding their participation on research or whether their situation prohibits them from exercise of free choice; and

- b. Whether confidentiality of participation and of data can be adequately maintained.

Prisoners should neither bear an unfair share of the burden of participating in research, nor should they be excluded from its benefits, to the extent that voluntary participation is possible.

Only certain kinds of research may involve prisoners as subjects:

- a. Studies (involving no more than minimal risk or inconvenience) of the possible causes, effects, and processes of incarceration and criminal behaviour;
- b. Studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or of prisoners as incarcerated persons;
- c. Research on particular conditions affecting prisoners as a class; and
- d. Research involving a therapy likely to benefit the prisoner subjects.

# **CHAPTER 7**

# **STUDY CONDUCT**

- 7.1 Data and Safety Monitoring**
- 7.2 Privacy and Confidentiality**
- 7.3 Compensation for Research-Related Injuries**
- 7.4 Audits and Inspections**
- 7.5 PI Self-Assessment Programme**

## **7.1 Data and Safety Monitoring**

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One of the review criteria for DSRB approval at initial review is that there is an adequate data and safety monitoring plan. All research proposals should include adequate provisions for monitoring of data collected for scientific validity and safety of research subjects. The monitoring plan for a particular research study would depend on the complexity of the research study and the possibility of potential harm to subjects.

### **Determination of Research Study Risk**

Determination of risk should include a consideration of both the interventions being performed and the research study population. Risk assessments must also take into account special circumstances that are unique to the research study such as disclosures of HIV status or results of genetic studies.

**MINIMAL RISK** – A research study is said to be minimal risk when the probability and magnitude of harm and / or discomfort are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Minimal risk studies generally include research involving surveys, questionnaires, blood samples; MRI scans without contrast agents, exercise testing in low risk populations, ECGs, and other such non-interventional studies.

**MODERATE RISK** – A moderate risk research study exceeds minimal risk, but would be less risky to the subjects than high risk research studies. Moderate risk studies may include clinical trials and observational studies using procedures with well-established risk profiles, behavioural trials, studies involving endoscopy, glucose-tolerance tests, skin or muscle biopsy, imaging requiring sedation etc. For example, a Phase IV trial or research studying efficacy of drugs for their indicated use.

**HIGH RISK** – High risk research studies include clinical trials on new drugs, approved drugs for off-label use, new medical devices, new surgical procedures, etc.

In general, research involving not more than minimal risk does not require a data and safety monitoring plan.

### **7.1.1 Safety Monitoring**

#### **I. Who Should Perform Safety Monitoring**

The data and safety monitoring plan should state who would assume monitoring responsibility. This will depend on the type and risk of the research study and may include the investigator, experts within the department or institution, independent consultants or a combination of the above. Some examples below:

- **Principal Investigator (PI)** – For a research study involving minimal risk to the subjects, it may be appropriate for the PI to manage the data and safety monitoring. Continuous close

monitoring by the PI may be an adequate and appropriate format for monitoring with prompt reporting of unanticipated problems involving subjects and others including serious adverse events to DSRB. For a minimal risk research study involving multiple sites, this function could be managed by the team PIs for each site or the lead / overall PI for the entire research study.

- INDEPENDENT EXPERT(s) or INDEPENDENT SAFETY MONITOR(s) (ISM) – For a moderate risk research study or investigator-initiated clinical trial involving single or multiple sites, or a study with endpoints that are not serious irreversible events, or the study's intervention effects are evaluated over periods of a few days to a few months or the study involves a smaller number of subjects whereby it can be completed quickly and the risk can be adequately assessed through simple comparisons. It is recommended that the data and safety monitoring be performed by an expert or group of experts in the disease and familiar with the agent being studied. Using an independent expert or team of experts is particularly helpful in monitoring of unblinded data for a double-blind research study, as this will help ensure a meaningful review by independent experts while maintaining study blinding amongst the research staff.
- DATA SAFETY MONITORING BOARD (DSMB) – DSMB is a committee that is established specifically to monitor participant safety and data throughout the life of a research study to determine if it is appropriate, from both scientific and ethical standpoints to continue the research study as planned. For high-risk studies and for sponsors or investigators- initiated large, blinded studies, involving multiple sites, it is recommended that a formal DSMB is appointed.

When appropriate, the scope of the DSMB's review could also include continuously reviewing and evaluating the efficacy of the study intervention, scientific validity and merit of the study, and data quality and integrity. Items reviewed by a DSMB can include:

- i. Interim or cumulative data for evidence of study-related adverse events;
- ii. Interim or cumulative data for evidence of efficacy according to pre-established statistical guidelines;
- iii. Data quality, completeness and timeliness;
- iv. Adherence to the protocol;
- v. Adequacy of compliance with goals for recruitment and retention, including those related to the participation of minorities;
- vi. Factors that might affect the study outcome or compromise the confidentiality of the trial data such as protocol violations, unmasking, etc. and
- vii. Factors external to the study such as scientific and therapeutic developments that may raise ethical concerns and/or impact subject safety.

For high-risk studies and for sponsors or investigators-initiated large, blinded studies, involving multiple sites, it is recommended that a formal DSMB is appointed.

- **COMPOSITION OF A DSMB** – This is a multidisciplinary committee that is usually composed of 3 to 6 experts in at least two areas; medical issues (the disease, drug, device, procedure, or outcome measure) and method issues (clinical trials design, data management, and statistical analysis).

The primary criterion for selecting DSMB members should be based on the respective member's expertise and experience. DSRB members could include:

- i. Expert(s) in research and biomedical ethics for trials with unusually high risks or with broad public health implications.
- ii. Epidemiologist(s), clinical pharmacologist(s), toxicologist(s) when such expertise appears important for informed interpretation of interim results
- iii. Individuals (often non-scientists) who may help bring to the DSMB the perspectives of the population under study
- iv. Representatives of the gender and ethnic groups, where appropriate.

When appointing DSMB members, the member's prior conflict of interest, if any, as well as commitment level should be considered.

- **ADDITIONAL CONSIDERATIONS WHEN DSMB IS REQUIRED** – The DSMB should consider the following factors when determining if a DSMB is required:
  - i. Study nature, design and procedures
  - ii. Size / scale of the study
  - iii. Study population
  - iv. Whether the study is a planned emergency research that is required to comply with 21 CFR 50.24(a)(7)(a)(4)
  - v. Practically of having a DSMB review
  - vi. Whether a DSMB will help assure scientific validity of the study
  - a. Examples of studies which may require DSMB include, but are not limited to the following:
    - i. Phase III clinical trials involving interventions that entail potential risk to the participants
    - ii. Studies involving high-risk procedures and/ or high expected rates of morbidity or mortality in the study population

- iii. Studies involving randomization and/ or blinding
  - iv. Studies involving multi-sites which may or may not involve a large study population
  - v. Studies involving new therapies (including devices) or science
  - vi. Studies involving a high chance of early termination
  - vii. Studies involving a vulnerable population (e.g., pediatric population, geriatric population, cognitively impaired persons)
- b. Examples of studies which may not require DSMB include, but are not limited to the following:
- i. Clinical studies with non-critical indications where patients are treated for a relatively short time (practical constraints) patients and the drugs under investigation are well-characterized and known for not harming patients.
  - ii. Early studies which are often exploratory in nature; and they are frequently not randomized or controlled, therefore accumulating results are known to the investigators and sponsors. Hence, issues regarding statistical interpretation of interim data, or confidentiality of interim data, are therefore generally less relevant in this setting.

## **II. Safety Monitoring Plan**

Monitoring should be planned to occur at specific points in time, such as quarterly, every six months or annually or after a specific number of subjects have been enrolled, or upon recognition of harm. The monitoring plan should state how often monitoring will be performed, who will perform monitoring and what data will be reviewed for safety monitoring.

The safety monitoring plan should include:

- a. Details of the assessments (laboratory tests, physical examinations, etc.) used to monitor for adverse events and the schedule of these evaluations.
- b. Description of anticipated events including character and expected incidence.
- c. Plan for grading the seriousness of events.
- d. Plan for assessing the causal relationship of events to the study and/or agent(s) being investigated.
- e. Persons responsible for assessing events.
- f. Persons responsible for managing events – the plan should identify the PI, co-investigators and / or other key personnel who are medically trained to manage the disease under study, as well as the procedures that impart more than minimal risk to

subjects. The plan should provide assurance that the PI will be on site to monitor the study subjects' safety on a daily basis.

- g. Persons responsible for reporting events according to DSRB guidelines.

### **III. Stopping Criteria**

An effective safety monitoring plan should be able to detect signals to decide when the research study should be stopped. Usually stopping criteria are based on one or more reasons such as:

- Efficacy – This occurs when there is high certainty that the research question has been answered. For example, when it is clear that one group is doing better than the others, or no group is likely to do better than any other.
- Futility – This occurs when it is evident that the research question will not be answered when the study is completed. For example, when too many subjects have withdrawn from the study, such that it is difficult to obtain conclusive data even though the study is continued.
- Safety – The risks of continued participation to subjects is too high.

### **IV. DSMB Reports**

When a clinical trial is subject to oversight by a DSMB whose responsibilities include review of adverse events, interim findings and relevant literature, the DSRB conducting the renewal process may request for and rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the DSRB.

However, the DSRB must still receive and review reports of local, on-site UPIRTSOs and any other information needed to ensure that its continuing review is substantive and meaningful. Evaluation reports other than that of a DSMB may also be accepted provided the evaluation meets the criteria listed above.

#### **7.1.2 Data Monitoring**

##### **I. Data Accuracy and Compliance**

The PI should describe the measures that will be taken to ensure accuracy of data and compliance to protocol. The extent and nature of monitoring should be based on considerations such as objective, purpose, design, complexity, blinding, size, and endpoints of the research. In general, there should be monitoring before, during and after the research.

- a. **Industry Sponsored Clinical Trials / Research Studies** – The PI is responsible for confirming with the Sponsor on the monitoring plan.

- b. **Investigator Initiated Clinical Trials Regulated by Health Science Authority (HSA)** – The PI is responsible for having a written monitoring plan prior to study initiation. Clinical trials should be monitored regularly by a monitor who is independent of the research team at this site, appropriately trained and should have adequate scientific/clinical knowledge. The monitor's qualifications should also be documented.

The PI may seek the assistance from their institution's Clinical Research Unit (CRU) / research office on finding a suitable monitor for their study. Some of the mechanisms by which monitoring can be achieved are:

- i. Cross monitoring by research coordinators working with different trials.
- ii. Research coordinators for same trial in different institutions cross monitor.
- iii. CRU may assign a senior coordinator as 'monitor' for PI-initiated studies conducted in the institution.
- iv. Research coordinators who usually coordinate industry sponsored studies may be assigned PI initiated studies to monitor.
- v. Engage an external vendor for monitoring services.

- c. **Studies Regulated by Human Biomedical Research Act (HBRA)** - For studies that fall under the scope of the HBRA, it is the responsibility of the Research Institution (RI) to supervise, review and proactively monitor these studies. The PI should contact their respective CRU to find out more about the proactive monitoring programme within their institution.

**For NHG Institutions:** For more information on the proactive monitoring framework for HBR studies conducted in NHG, please go to NHG Research Website <https://www.research.nhg.com.sg> > Ethics & Quality > Research Quality > Monitoring.

## II. Monitoring Plan

The monitoring plan should consist of a description of the monitoring strategy, the monitoring responsibilities of all parties involved, the monitoring methods and monitoring of the critical data and processes. The plan should be tailored to human subject protection and data integrity risks of the study. The monitoring plan should also reference the applicable policies and procedures.

Sponsor / PI should determine how the outcome of data and safety monitoring are communicated to other participating study sites, as well as to the DSRB (where applicable).

*The monitoring plan template is available for download at NHG Research Website <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOP & Templates.*

## **7.2 Privacy and Confidentiality**

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Personal information is any identifiable information about an individual. It not only includes personal particulars, but also details of medical conditions, as well as information disclosed or derived in the process of healthcare management. In the research context, it will include any information collected, used or generated as part of the research process.

Protecting the privacy of research participants and the confidentiality of their personal information obtained or derived from research is based on the principle of respect for persons. Thus, personal information should be stored and managed in ways that provide proper security and confidentiality.

Researchers should also ensure all necessary approvals (as per institution requirements) are obtained before accessing and using personal information for research. The patient must also give prior written consent for such access, unless the IRB has granted a waiver of consent.

### **7.2.1 Determining if Data is Identifiable**

When determining if data is considered identifiable, researchers should consider if the data itself or from that data and other information to which the researcher or organisation has or is likely to have access to can lead to the identification of an individual.

Individually-identifiable in relation to human biological material or health information pertaining to an individual, means that the individual can be identified:

- i. From the human biological material or health information; or
- ii. From that human biological material or health information and other information to which the person, research institution, tissue bank or other organisation has or is likely to have access.

De-identified data refers to data that is lightly processed and coupled with appropriate data safeguard measure to reduce the risk of re-identification of data subjects.

*You may refer to the HealthTech Instruction Manual (HIM) <https://www.moh.gov.sg> > All Healthcare Professionals > HealthTech Instruction Manual and the PDPC Guide to Basic Data Anonymisation Techniques at <https://www.pdpc.gov.sg> > Help and Resources > Guide to Basic Data Anonymisation Techniques for more information.*

### **7.2.2 Use of Subject Identification Codes**

Data collection forms (DCFs) and Case Report Forms (CRFs) should not contain information directly identifiable to a subject (such as name, identity card number, address, etc.) unless it is to be used as a source document.

Each subject should be assigned a unique subject identification code to be used on DCFs, CRFs, serious adverse event reports, UPIRTSOs and any other research-related data. In

addition to the subject identification code, subject initials may also be entered. The link between the subject identification code and the subject identifiers should be stored in a separate document.

In some instances, a combination of data elements collected on DCFs / CRFs may potentially identify a subject. Care should be taken to ensure that the information collected is appropriately coded such that it cannot be traced back to the individual without the linking code unless it is to be used as a \*source document.

*\*Source document are documents that have source data, including original documents, data, and records (such as hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X rays, subject files, and records kept at pharmacy, at the laboratories, and at medico-technical departments involved in the research).*

### **7.2.3 Use of Anonymised Data**

Anonymised Data refers to data that is heavily processed to the extent that it is very unlikely a unique individual can be re-identified evidently (spontaneous re-identification), or through attempts to match with other identifiable datasets or publicly available information.

Researchers should seek to use anonymised data for their research or for datasets to be processed for statistical outputs to safeguard patient or participant confidentiality from exposure or loss as far as possible. \*De-identified data could be used for data analysis purpose with consent from research subjects. The use of anonymised data is outside the scope of the PDPA.

Researchers can obtain anonymised data from their institution's information management team or equivalent (e.g., Trusted Third Party). Data would not be considered anonymised if there are serious possibility that an individual could be re-identified, taking into consideration both:

- a. The data itself, or the data combined with other information to which the institution has or is likely to have access; and
- b. The measures and safeguards (or lack thereof) implemented by the institution to mitigate the risk of identification.

The reversibility of the specific process used would be a relevant consideration for institutions when managing the risk of identification.

*You may refer to the PDPC Guide to Basic Data Anonymisation Techniques at <https://www.pdpc.gov.sg> > Help and Resources > Guide to Basic Data Anonymisation Techniques for more information.*

#### **7.2.4 Data Protection**

Individuals conducting research should take all reasonable steps and safeguards to protect personal information against accidental or unlawful loss, modification or destruction, or unauthorised access, disclosure, copying, use or modification.

Individuals should not attempt to re-identify anonymised information or biological material, or disclose any individually-identifiable information of a research subject except:

- a. With the consent of the research subject or the person authorised to give consent on the research subject's behalf
- b. When it is necessary to do so in connection with the administration or execution of anything under the HBRA;
- c. When ordered to do so by a court;
- d. Where the information on the identity is publicly available;
- e. For the purposes of providing the identity/information to any person or class of persons to whom, in the opinion of the Ministry of Health (MOH), it is in the public interest that the information is disclosed;
- f. Where it is permitted or provided for under the HBRA or any other written law or rule of law; or
- g. In such other circumstances and to such persons as may be prescribed.

Individual receiving individually-identifiable information of human biological material of a research subject should not disclose any individually-identifiable information of the research subject, if at the time when the individuals receiving the information or material, they know or had reasonable grounds to believe that it had been communicated or supplied to them in a manner which breaches the HBRA or any other applicable law.

#### **7.2.5 Data Management**

The Principal Investigator should ensure the following:

- a. The Study Responsibility Log clearly states who in the research team is responsible for data management activities such as transcription of data to CRFs, data entry, and analysis (where applicable).
- b. The research data is recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

- c. The databases (for data analysis) should not contain subject identifiers. The data linking subject identifiers and the subject identification codes should be stored separately.
- d. All personal data files (containing patients' name, NRIC etc.) must be protected with strong passwords as per Healthtech Instruction Manual-Data Management (HIM-DM), e.g., minimally 12 alphabets, includes upper and lower case, mixture of numbers and symbols and cannot include the personal information (e.g., name, NRIC).

### **Use of Research Data Capturing Tools and Application**

- a. The Research Electronic Data Capture system (e.g., REDCap) is recommended as a data capture tool.
- b. FormSG may also be used as a data capturing tool.
- c. Researchers should check their institution policies to ensure that the data capture tool used in all research (including industry sponsored studies) is acceptable and meets institution requirements, e.g., comply with Synapxe or equivalent security recommendation, obtain approval to use alternative platforms.
- d. Private and public Cloud & Google Drive should not be used to capture Patients' Personal Data. Only corporate approved Cloud services (i.e., H-Cloud) is allowed.
- e. The access to shared drive folders containing research data files must be restricted to authorised personnel only.

### **Storage of Research Data**

- a. Corporate approved secure data storage facilities managed by Synapxe, Storage Area Network (SAN), Sharepoint or equivalent and institution endorsed systems should be used for the storage of research data.
- b. Research data stored in hardcopy form (e.g., study documents, data collection form, etc.), should minimally be locked in storage units within institution's premises and only accessible by authorized study team member.
- c. Users should consider the following storage options for storage of research data and research documents.
  - i. Only authorised corporate devices should be used, and these should be for specific circumstances. For example, to transfer data between computers and when sharing data with collaborators or individuals beyond the institution network.
  - ii. Corporate issued storage devices should only be accessed and used by authorized persons. Personal hard disks or thumb drives are unauthorised and should not be utilized.

- iii. Institutions are strongly recommended to track the issuance and use of corporate issued devices (external hard disk and thumb drives). Issuing institutions are accountable for any loss of these devices.
- iv. When the data is stored in an external device (corporate issued hard disk or thumb drive), subjects' identifiers should never be stored in the same device.
- d. Users are to abide and follow the on-site and off-site requirements in the HIM-DM and all other relevant regulations and guidelines.
- e. Individual issued with corporate devices are accountable for the proper usage and will need to report to the institution for any loss and non-compliances.

For industry sponsored research, data management at the site is usually restricted to transcribing information on case report forms, whether paper based or electronic and answering data clarification queries.

- a. The PI should endorse any changes or corrections made in the CRFs by sponsor's designated representatives. The PI should retain records of the changes and corrections.
- b. The PI must ensure the accuracy, completeness, legibility and timeliness of data reported to the sponsor in the CRF and data queries are replied to in a timely manner.

**For NHG researchers:** You are strongly encouraged to use REDCap (E.g. NHG REDCap) for data capturing. Alternatives could be explored, but they must comply with IHIS security recommendation. Please refer to NHG Research Website <https://www.research.nhg.com>) > Home > Resources > NHG Research Database Platform (REDCap) for more information.

### 7.2.5 Transferring/ Releasing / Sharing of Research Data

The organisation transferring data must take appropriate steps to ensure its own compliance with the data protection requirements in the PDPA while the personal data to be transferred remains in its possession or under its control. The orgnaisation should also comply with its own requirements on data transfer (e.g., seek approval from institution Data Exchange Office (DXO) prior to any data transferring/sharing).

The transferring organization must also ensure that it has taken appropriate steps to ascertain whether, and ensure that, the overseas recipient is bound by legally enforceable obligations to protect the personal data to a standard comparable to the PDPA. Legally enforceable obligations include those imposed under:

- a. Any law;
- b. Any contract that imposes an obligation on the overseas recipient to protect the personal data to a standard comparable to the PDPA, and which specifies the countries to which the personal data may be transferred; or
- c. In the case of data transfers between related organisations, any binding corporate rules imposing an obligation on the overseas recipient to accord the personal data

protection to a standard comparable to the PDPA and specifies the recipient, the countries to which the personal data may be transferred and the rights and obligations under the corporate rules.

- d. Any other legally binding instrument.

Alternatively, the transferring organisation can be considered to have taken such appropriate steps if-

- a. The individual gives consent.

However, this is provided that:

- (i) The individual has been given a reasonable written summary of the extent to which the personal data will enjoy protection comparable to that under the PDPA;
  - (ii) The transfer of personal data is reasonably necessary to provide a product or service to the individual; and
  - (iii) The transferring organisation did not give the individual false or misleading information about the transfer;
- b. The transfer is necessary to perform a contract between the individual and the transferring organisation; or
  - c. The transfer is necessary to conclude or perform a contract between the transferring organisation and a third party if -
    - (i) The contract is entered into at the individual's request or
    - (ii) If a reasonable person would consider the contract to be in the individual's interest.

Research Agreements should be in place to capture the sharing of research data. Each institution may determine the form of documentation to record the sharing of research data. Institutions could take guidance from PDPC's Guide on Data Protection Clauses for Agreements relating to the Processing of Personal Data.

Where the research data arise from joint collaboration and are not owned solely by one institution, the sharing of such research data should be with the express consent and agreement from the other data co-owner(s).

The sharing of research data should take into consideration the funding terms and conditions and any other rights or restrictions on the ownership, use and disclosure of such research data, where applicable.

Researchers who intend to share research data with journals or public data repositories must ensure:

- a) They obtain the approval from the institution prior to each submission;
- b) Data shared is anonymized and only data that is used to derive the conclusions in the publication is shared; and
- c) Comply with the relevant institution policy and guidelines.

## **7.2.6 Management of Research Data Upon Study Completion**

Study teams must retain research data for a minimum retention period. At present, the minimum retention period of research data is 6 years. Study teams may retain research data for a longer period, where it is specifically indicated. For example, within the institution policy, Research Collaboration Agreement (RCA) or Clinical Trial arrangements.

If there is a potential use of the data for future research, the study team should register it as a standing database in accordance with institutional requirements.

If the research data is no longer required at the end of the stipulated minimal archival period, the research data should be destroyed according to institutional disposal policies. A documentation of destruction should be maintained.

## **7.2.7 Research Data Breach Management**

A data breach generally refers to the accidental and/or intentional unauthorized access and retrieval of information that may include corporate and personal data.

In the event of a research data breach, researchers should report the breach in the accordance to their institution policy (e.g., NHG Research Data Policy).

## **7.2.8 References and Further Reading**

**For Non-NHG institutions:** Please refer to your institution specific requirements and policies governing data.

**For NHG institutions:** NHG researchers should adhere to the **NHG Research Data Policy** and other applicable institutional requirements to ensure that research data is appropriately managed.

You may access the **NHG Research Data Policy** via NHG Website <https://mynhg.nhg.com.sg> > Home > Group Research > Research Compliance Unit > Research Data Policy.

## **7.3 Compensation for Research-Related Injuries**

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### **7.3.1 General Principles**

- a. The CIOMS International Ethical Guidelines for Biomedical Research Involving Human subjects states that investigators are responsible for ensuring that research subjects who suffer injury as a result of their participation should be entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap.

- b. The DSRB's stand is that lack of compensation for medical care to individuals who are injured as a result of their involvement in a research study is indefensible because it is against the ethical principle of justice. Thus in good faith, compensation (i.e. medical treatment of research-related injuries) should be provided for all research subjects who suffer a research-related injury. The investigator's institution may purchase clinical trial insurance and medical malpractice insurance to provide for such compensation.

### **7.3.2 Guidelines for Subject Compensation for Research-Related Injuries**

In general, institutions (and / or sponsors) should pay for medical treatment of any injuries arising from participation in the research as long as the injury is related to participation in the research and the injury is not a consequence of an existing condition or standard clinical care and standard diagnostic procedures.

Several exclusions may be acceptable, depending on the nature of injury, study, subjects, etc. For example:

- a. Compensation may be paid for only serious injury of an enduring and disabling character and not for exacerbation of an existing condition or temporary pain or discomfort, or less serious or curable complaints.
- b. Compensation need not be paid for the failure of a medicinal product to have its intended effect or to provide any other benefit to the patient; or to patients receiving placebo in consideration of its failure to provide a therapeutic benefit.
- c. Compensation need not be paid when injuries arise due to non-compliance with the trial protocol on the part of the subject.

The institution must remain responsible to compensate for injuries resulting from negligence / non-compliance by the research team.

For the avoidance of doubt, these recommendations are not intended to discourage or prevent investigators (and / or sponsors) from providing further or additional compensation to subjects if they feel that it is appropriate to do so.

For sponsor-initiated studies:

- a. Sponsor-initiated studies often follow the ABPI guidelines for compensation of research-related injuries.
  - i. ABPI's Guideline for Medical Experiments in Non-Patient Human Volunteers (for Phase I studies).
  - ii. ABPI's Clinical Trial Compensation Guidelines (for Phase II and III studies).
- b. The DSRB may accept alternative guidelines of compensation to research subjects, if the terms provide equal to or more protection than that provided by the ABPI guidelines.

Research subjects should be adequately informed of compensation guidelines applicable to them and the limitations (if any). In addition, the PI is encouraged to actively provide a copy of the ABPI guidelines to the research subjects.

- c. Depending on the nature of the study, risks and population involved, the DSRB may require additional provisions of compensation.

### **7.3.3 Informed Consent Process and ICF Language**

Research subjects should be adequately informed of compensation guidelines applicable to them and the limitations of these (if any). This can be done via the inclusion of a compensation statement in the ICF.

The recommended wording for the compensation statement is provided in the NHG DSRB Informed Consent Form Template.

*The NHG DSRB Informed Consent Form Template is available for download at NHG Research Website <https://www.research.nhg.com.sg>) > Resources > Ethics Forms & Templates.*

## **7.4 Audits and Inspections**

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### **7.4.1 Preparing for Audits and Inspections**

Upon receiving notice that an audit / inspection is to be scheduled, the PI should inform the Director / designee of Research where appropriate, the purpose, time and date of the audit / inspection. If the research team receives a notice for an inspection, the PI should inform the sponsor and all individuals and groups involved in the conduct of the study, if any, as soon as possible.

The PI / designee should ensure that all documentation, including ICFs, source documents, DCFs / CRFs, and the investigator files for the study are accurate, complete and available for review by the auditor(s) / inspector(s).

The clinical research coordinator / study pharmacist should ensure that the investigational product accountability records are accurate, complete and available for review. If there had been any instances where an emergency breaking of the blind was required, the documentation would have to be made available.

The PI / designee should ensure that documentation on collection, shipment, receipt and storage of biological specimens is accurate, complete and available for review.

The PI / designee should ensure that all records of staff qualifications, research-related training and protocol-related SOPs are available for review by the auditor(s) / inspector(s).

The PI should ensure that key study team members are available for a meeting with the auditor(s) / inspector(s) on the day of the audit / inspection.

Where requested by the auditor/inspector, the PI should provide relevant documents for pre-audit review in a secure manner (e.g., password protected via corporate email).

*You may refer to the Investigator File Contents Template and Pre-Audit Checklist available at <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOP & Templates, to help you prepare for an audit / inspection.*

#### **7.4.2 During The Audit / Inspection**

The PI should meet with the auditor(s) / inspector(s), provide orientation and access to the study records and files, as well as provide copies of requested study-related documents.

The PI should ensure that questions posed by the auditor / inspector are answered by the appropriate study personnel.

Possible questions that may be asked during the audit / inspection:

- a. What is your research topic?
- b. What are the inclusion and exclusion criteria?
- c. Describe the screening method used to determine subjects' eligibility and who implements the screening process.
- d. How are prospective subjects identified for the project, i.e. what are your recruitment strategies?
- e. Describe the mechanisms you have in place to ensure that each subject meets the stated inclusion / exclusion criteria and that all study procedures are implemented as written. Do you document the eligibility assessment in the source documents (e.g. medical records)?
- f. Once a prospective subject is identified, describe the procedures by which informed consent is obtained from a subject. Who is the person responsible for taking informed consent?
- g. Who addresses questions presented by the subject or subject's family?
- h. What is the time interval between the presentation of the research study information and the actual signing of the ICF?
- i. Who are the study team members and what are their responsibilities in the study? Are the study team members trained and are trainings documented?
- j. What are the study procedures and how are they performed? Are the study visits and procedures documented?

- k. What is the procedure for the management of investigational product (IP)? Is there an IP management workflow / SOP and documentation of IP accountability?
- l. What is the procedure for randomisation and unblinding?
- m. How are the biological specimens managed? Is there a biological specimen management workflow / SOP and a biological specimen log to track collection / storage / transfer / use / disposal etc.?
- n. Is refrigeration required for biological samples? If yes, is a temperature log and equipment maintenance / calibration log maintained?
- o. How long will the samples be stored?
- p. Do you maintain an investigator file for this study?
- q. Do you have case report forms / data collection tools developed for this study?
- r. How do you handle (e.g., store, monitor) the data collected?
- s. Where are your research records stored?
- t. What mechanisms do you have in place to protect the confidentiality of your subjects?
- u. How frequently is the study data reviewed, i.e., per subject, per month etc.?
- v. How would you handle an unexpected event such as the loss of research records or study data?
- w. How do you deal with unanticipated problems involving risks to subject and others?
- x. What additional mechanisms do you have in place to protect subjects in your research?
- y. What do you do if you receive a complaint from a subject? If you are unable to resolve the issue – what do you do?
- z. Describe your oversight of the study and the communications that occur regarding this study, i.e. do you have weekly meetings? Are the meetings documented?

At the end of the audit / inspection, the PI and key study team members should participate in the closing meeting with the auditor(s) / inspector(s).

*You may refer to the NHG Research Quality Management (QM) Study Review Checklist available at <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOP & Templates, to help you prepare for an audit / inspection.*

### **7.4.3 After The Audit / Inspection**

The audit / inspection report will be sent to the PI on a communicated date after the audit / inspection, detailing the findings. The PI, in collaboration with the study team members, will be required to formulate a CAPA in response to the audit / inspection report. The CAPA should detail the measures implemented or steps taken to address each finding. The completed CAPA should be sent back to the auditor / inspector by the stipulated deadline.

*The Corrective Action & Preventive Action Plan (CAPA) Template is available for download at <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOP & Templates.*

## **7.5 PI Self-Assessment Programme**

The PI Self-Assessment Programme is a quality assurance component under the NHG OHRPP Research Quality framework. This programme familiarises investigators with the requirements of proper research conduct and identifies areas in their conduct of research that may require improvements.

The PI Self-Assessment Form (PISAF) is a tool used to facilitate self-monitoring and is an effective way for investigators to assess if the research study has been conducted in compliance with applicable regulations and guidelines.

The NHG Research Quality Management (RQM) unit would select PI(s) to complete the PISAF based on specific criteria such as experience of the PI and study risk level (e.g., expedited or full board review study). Selected PIs would be notified through email to complete the PISAF.

RQM will review the completed PISAF and make recommendations or issue queries on any aspect(s) of the study conduct that may require improvement. PI would be required to respond to queries issued by RQM within a stipulated timeline.

*The PISAF is available for download at <https://www.research.nhg.com.sg> > Resources > Proper Conduct of Research SOPs & Templates.*

*For more information, you may refer to the PISAF FAQ available at <https://www.research.nhg.com.sg> > Ethics & Quality > Research Quality > PI Self-Assessment.*

# **CHAPTER 8**

# **STANDING DATABASES**

**8.1 Standing Databases**

**8.2 Responsibilities of Custodians**

**8.3 Consent for the Storage of Data for Future Use**

**8.4 Data Management**

## **8.1 Standing Databases**

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### **I. Definitions**

**Standing Database (SDB)** - Contains electronic data stored as a potential resource for future research.

**Owner** The institution / cluster is the owner of the database set up by their staff member for the purposes of future research.

**Custodian** Any individual appointed by the data owners to be the overall person responsible for the set-up, conduct and maintenance of a standing database.

**Database Team Member** Any individual member of the standing database team designated and supervised by the custodian to perform database-related activities that may or may not involve participant contact (e.g., database administrators).

**Department Representative / Head of Department (DR / HOD)** Endorsement to ensure traction over the collection and storage of data and that the department can adequately support the set-up, maintenance and closure of the SDB.

**Institution Representative (IR)** Endorsement to ensure the custodian knows the institutional and legal responsibilities and is compliant to the institution policies.

**Institutional Review Board (IRB - DSRB)** Acknowledgement and review to ensure that the recruitment and consent process of the participants complies with ethics requirements & regulations.

**Research Data Institutional Deputy (ID)** The ID is appointed by the PIC to provide an independent and timely review of standing database applications and grant approval for the establishment of standing database in his/her institution.

**Research Data Secretariat (RDS)** The secretariat provides support to the NHG Principal Person-In-Charge (PIC) to oversee cluster policies and procedures on the use and management of research data.

**Principal Person-In-Charge (PIC)** PIC is responsible for ensuring that all research data related activities comply with legislation, the Human Biomedical Research Act (HBRA), the Personal Data Protection Act (PDPA) and Healthtech Instruction Manual (HIM).

## **II. Considerations When Setting up a Standing Database (SDB)**

The procedure for setting up the database and subsequent acquisition of data should be written and adhered to. This should include (but not limited to):

- a. A list of names and designations of the custodians and personnel given access to the database. This “access list” should be updated regularly. Access to the database should be restricted to authorized personnel only and should be supervised closely by the appointed custodian and kept to a justifiable minimum.
- b. A description of the types, sources, method of collection, storage, transfer, retention and disposal of the data.
- c. Information on the consent process or justifications for a waiver of informed consent.
- d. Security measures used to maintain confidentiality of data.
- e. A description of the process to ensure that individual research studies utilizing data from the database will not be conducted without IRB and Institutional authorities’ review.

Where there is shared ownership of a database amongst various NHG or Non-NHG institutions, the owners should agree upon the most suitable custodian.

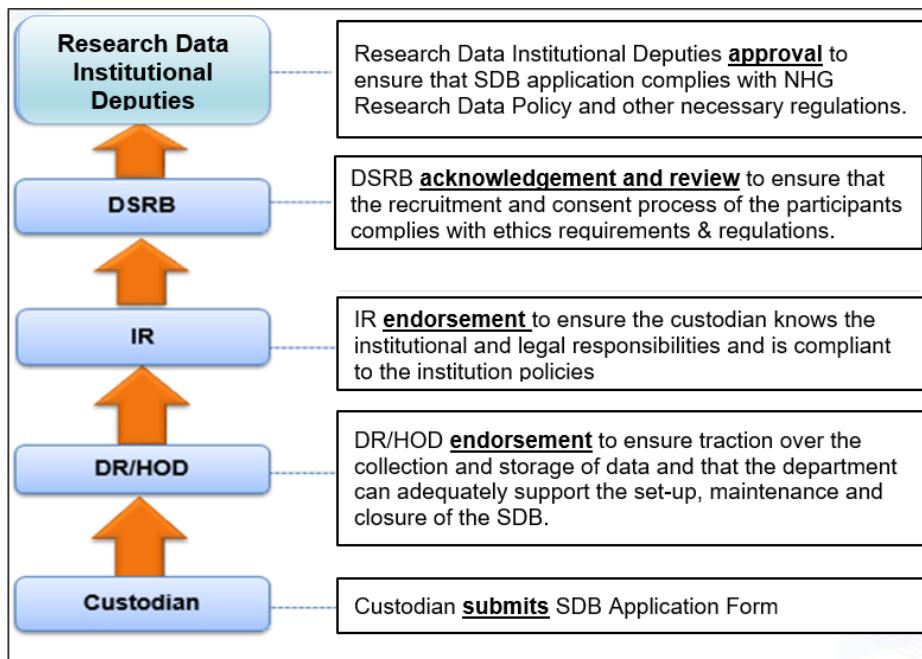
## **III. Registration of Standing Databases**

Databases that are created with the intention of using the stored data for future research should be registered as a Standing Database (SDB). Databases which are created as part of a previous IRB approved research study that has since been completed, may be set up to store data for possible research. Such databases should be registered as a SDB upon completion of the research study. Prior permission must be sought from the relevant institutional authorities before the setting up of SDBs.

**For Non-NHG Institutions:** Custodians would need to adhere to their own institution requirements when setting up SDBs and are also encouraged to submit a Standing Database Application to their ID equivalent for review and approval.

**For NHG Institutions:** With effect from 01 August 2020, all new SDBs and amendments must be approved by NHG Research Data Institutional Deputies (IDs), before proceeding with SDB activities. Table 14 below reflects the review process for NHG SDB applications.

Table 14 – NHG Standing Database Applications Review Process<sup>1</sup>



The custodian and database team members must also disclose any real or apparent conflict of interest in the application form to the ID.

## 8.2 Responsibilities of Custodians

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Custodians are responsible for the proper collection, use and disclosure of data, including the release of data from these standing databases for research. Responsibilities of a Custodian include (but not limited to):

- The custodian must be in the permanent employment of an institution under NHG. Ensure he / she is qualified by education, training and experience to assume responsibility of managing a standing database. He/she must also maintain an up-to-date curriculum vitae. For NHG custodians, he / she must be in the permanent employment of an institution under NHG.

<sup>1</sup> You may refer to NHG Research Website (<https://www.research.nhg.com.sg/>) > Conducting Research > Research Data Management > Standing Databases (SDB) for more information.

- b. Maintain a list of persons to whom he/she has delegated significant database related responsibilities.
- c. Appoint adequate qualified staff to properly manage the standing database.
- d. Ensure that all persons assisting with the conduct of the database are adequately informed about the collection, use and disclosure of the data as well their duties related to the management of the standing database.
- e. Disclosure of any potential conflict of interest between, Custodian and / or Data Team Members with the participants in the application of the Standing Database or during the duration of the Standing Database.
- f. Ensure compliance with Standing Database Application approved / acknowledged by applicable parties (e.g. IR, IRB, ID). Deviations from or changes of the project should not be implemented without prior review and documented approval / acknowledgement applicable parties.
- g. Manage, access and utilize data in a manner that is consistent with their institutional policies and applicable regulatory requirements.
- h. Ensure recruitment of participants is in a fair and equitable manner.
- i. Ensure that informed consent is obtained from potential participants prior to their enrollment into the standing database, unless consent is waived by applicable parties (e.g. IRB). The most current consent document must be used to obtain consent.
- j. Maintain all relevant documents and allow audits / inspects of such records from applicable parties.
- k. Ensure accuracy and completeness of data in all case report forms and all standing database related documents.
- l. Ensure that applicable approvals are obtained prior to allowing a third party to access / utilize the standing database.
- m. If the custodian is going away for a long time, the standing database should be formally transferred to another custodian. Should the custodian be leaving the employment of the institution, another employee should be appointed as the new custodian by the institution, as the custodian does not possess any ownership of the database. The incoming individual should be qualified and assumes all the responsibilities as the custodian.

- n. The custodian should inform the owner(s) and relevant parties (e.g., NHG ID) when the database has ceased to be useful and is therefore decommissioned.

**For Non-NHG Institutions:** Custodians would need to adhere to their own institution requirements for standing database maintenance.

**For NHG Institutions:** After ID's initial approval, the custodian should continue to comply with the following:

- a. Submit standing database status reports to the ID before the expiry date of the approval.
- b. Report non-compliances, deviations as well as suspected data breaches to ID and other authorities, where relevant, in accordance with institutional requirements.
- c. Custodians who will be away for more than 6 months would need to formally transfer the standing database to another custodian. This change should be reviewed and approved by the ID.

NHG custodians should refer the **NHG Research Data Policy**<sup>2</sup> and applicable institution requirements for more information on how research data should be managed.

### **8.3 Consent for the Storage of Data for Future Research**

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**INFORMED CONSENT** - For databases that are intended for use in possible future research (regardless of whether the primary function is for research or not), informed consent from participants should be obtained. Custodians are to ensure that all required consent elements are present in the Informed Consent Form provided to participants.

If the stored data is planned to be used in future studies regulated by the Human Biomedical Research Act (HBRA), the Informed Consent Form must contain all the Section 12 (1) appropriate consent elements of the HBRA.

**WAIVER OF INFORMED CONSENT**- In certain circumstances the requirement to obtain informed consent may be waived. The custodian must be able to justify the criteria for a waiver of informed consent for the standing database in their submissions to IRB/ID.

*For more information on informed consent, please refer to Chapter 5 Informed Consent.*

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<sup>2</sup> You may refer to <https://mynhg.com.sg> > Group Research > Research Compliance Unit for a copy of the NHG Research Data Policy

## **8.4 Data Management**

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### **8.4.1 Confidentiality**

Harm that may occur because of database activities are mostly related to threats to privacy and breaches in confidentiality. There should be policies and procedures in place to ensure adequate protections for privacy and maintenance of confidentiality. Such procedures should regularly be reinforced by the appointed custodian to all personnel who have been granted access to the standing database. Owners and appointed custodians of standing databases may undertake regular internal audits to monitor compliance with these guidelines and to ensure that there are adequate protections put in force.

The confidentiality of the private information contained in the databases is primarily the responsibility of their respective custodians. Custodians need to put in place data security features to prevent and monitor regularly for unauthorized access to the database. Such precautions could range from structural or IT-based solutions features (e.g., installation of firewalls, encryption or password protection) to organizational and administrative measures (e.g. regular audits).

Databases should be stored in secured corporate issued computers / laptops / storage media. These computers/laptops/storage media must be password protected, and stored under lock and key (e.g., in a locked cupboard/ office). There should be scheduled changes (e.g., at least every 6 months) of passwords.

Owners and custodians are responsible for taking active steps to ensure that all staff who are given access to the database as part of their work, maintain the confidentiality at all times. They must also ensure compliance with their respective institutions' research data management policies (e.g., NHG Research Data Policy).

### **8.4.2 Utilisation of Stored Data**

Each subsequent research study (including studies initiated by the custodian and all staff listed in the "access list") utilising any standing database will require prior approval from IRB before study initiation. The concurrence of the custodian should also be obtained.

Depending on the nature of the study, IRB and / or ID will determine if access to the standing database may require additional consent. Some considerations by the IRB will include whether any patient contact is proposed, the practicability of getting informed consent for the research and whether the data extracted and used for the research will be de-identified or aggregated etc.

In general, recipients of the data should not be provided with identifiable information or to information through which identities of patients or subjects may be readily ascertained.

#### **8.4.3 Disposal of Stored Data**

When the database is no longer required (with agreement from custodian, data owner, and applicable parties), all data and identifying links must be destroyed according to institutional disposal policies. Documentation of destruction (e.g., by whom and when was the destruction) should also be maintained.

The actual destruction of Classified materials shall be witnessed by appropriate Entity personnel, especially where Classified data may be viewed by unauthorised individuals during the disposal process<sup>3</sup>.

Documentation of the Classified material, destruction process, and declaration by the destruction personnel and witness shall be kept for a period of at least 3 years<sup>4</sup>.

#### **8.4.4 Retention of Research Data**

Study teams must retain research data for a minimum period. Currently, the minimum retention period of research data is 6 years. Study teams may retain research data for a longer period, where it is specifically indicated.

Should the owner deem it necessary to archive the database for future reference, the owner should continue to comply with the guidelines for the storage of data. The owner shall be responsible for the safekeeping of archived database.

#### **8.4.5 References and Further Reading**

**For Non-NHG institutions:** Please approach your respective institutions on their research data policies.

**For NHG institutions:** NHG Custodians should adhere to the **NHG Research Data Policy** and other applicable institutional requirements to ensure that their standing database is appropriately managed.

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<sup>3</sup> Healthtech Instruction Manual-DM (M6.11.5-R)

<sup>4</sup> Healthtech Instruction Manual-DM (M6.11.6-R)

# **CHAPTER 9**

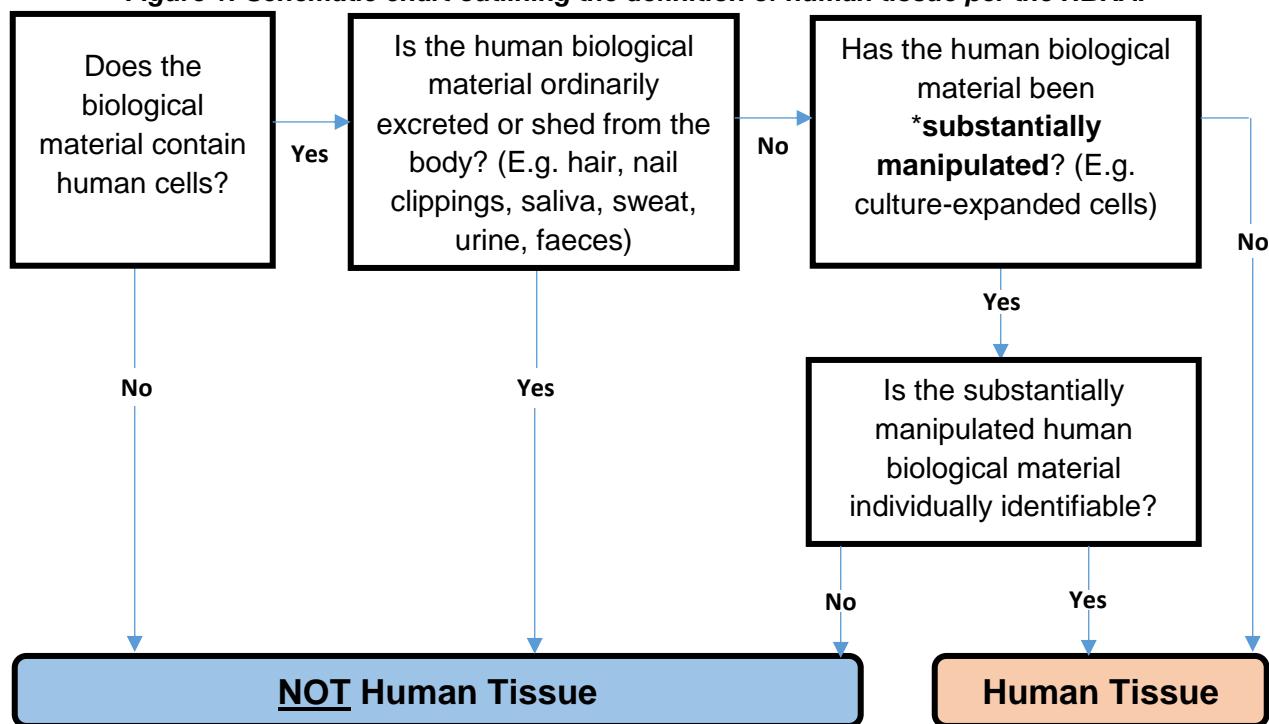
# **TISSUE BANKS**

- 9.1 Definition of Human Tissue, Tissue Bank and Tissue Banking Activities**
- 9.2 Tissue Bank Registration**
- 9.3 Key Human Tissue Framework Requirements**
- 9.4 Serious Adverse Event/ Untoward Occurrence Reporting**
- 9.5 Suspected Offence Or Contravention (SOC) Reporting**
- 9.6 Cessation of Tissue Bank Operations**
- 9.7 Submissions to the NHG Tissue Compliance Committee (TCC) (Applicable to NHG Institutions only)**
- 9.8 Tissue Bank Essential Documents**

## 9.1 Definition of Human Tissue, Tissue Bank and Tissue Banking Activities

The Human Biomedical Research Act (HBRA) 2015 defines **Human Tissue (HT)** as any biological material obtained from the human body that consists of, or includes, human cells but excludes human biological material specified in the First Schedule of the HBRA. This is summarized in **Figure 1**.

**Figure 1: Schematic chart outlining the definition of human tissue per the HBRA.**

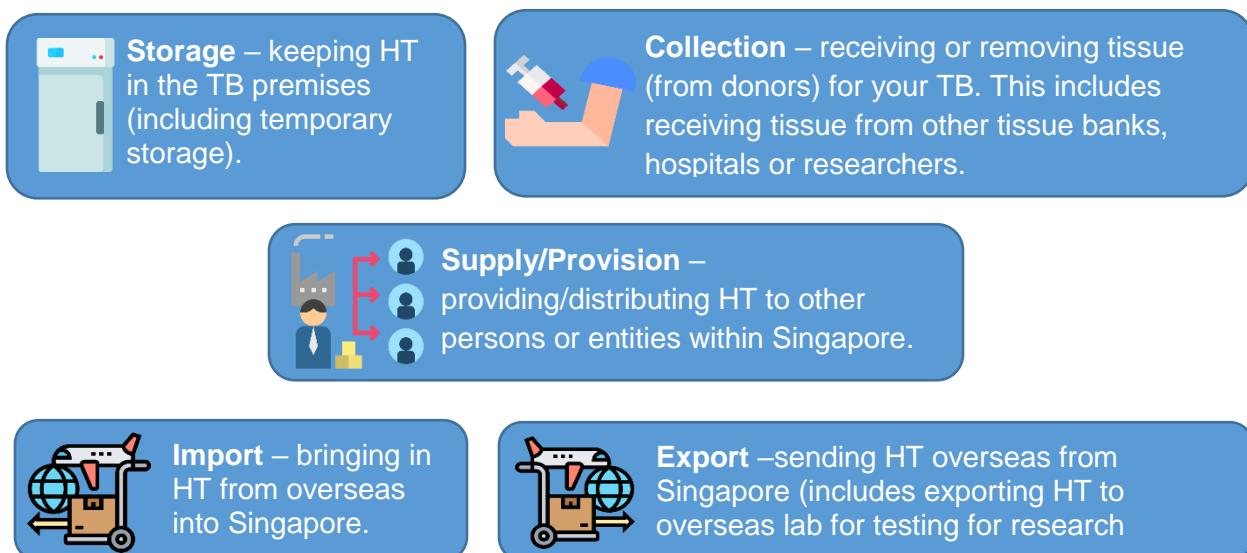


\*A sample is considered to be substantially manipulated if it has been processed in a manner such that its functional, structural and biological characteristics are substantially manipulated as compared to the time of collection from the donor. Processes that would not be considered to be substantial 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.

A **Tissue Bank (TB)** refers to an individual or a body of persons, whether corporate or unincorporate, or other organisation, that carries on or conducts any tissue banking activity. However, tissue banking activities which is solely for the purpose of the person's or organization's own research, which falls within any of the following descriptions, would not be considered a TB:

- a. National public health research as defined in and conducted in accordance with section 59A of the Infectious Diseases Act (Cap. 137);
- b. Clinical trials (CT) of health products conducted in accordance with the Health Products Act (Cap. 122D);
- c. Clinical trials of medicinal products conducted in accordance with the Medicines Act (Cap. 176);
- d. Human Biomedical Research (HBR) regulated under the HBRA (HBRA Section 37 - Restrictions on activities relating to human tissue, will still apply).

**Tissue banking activity** refers to a structured and an organized 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:



Despite the above paragraph, tissue banking activities exclude the following:

- a. Institution-based central laboratories that are set up for the primary purposes of clinical diagnosis or therapeutic treatment and not conducting tissue banking activities as described above.
- b. Tissue banking activities as part of contracted duties solely to support a clinical trial or HBR (e.g. Contract Research Organisations (CROs), processing laboratories).

## **9.2 Tissue Bank Registration**

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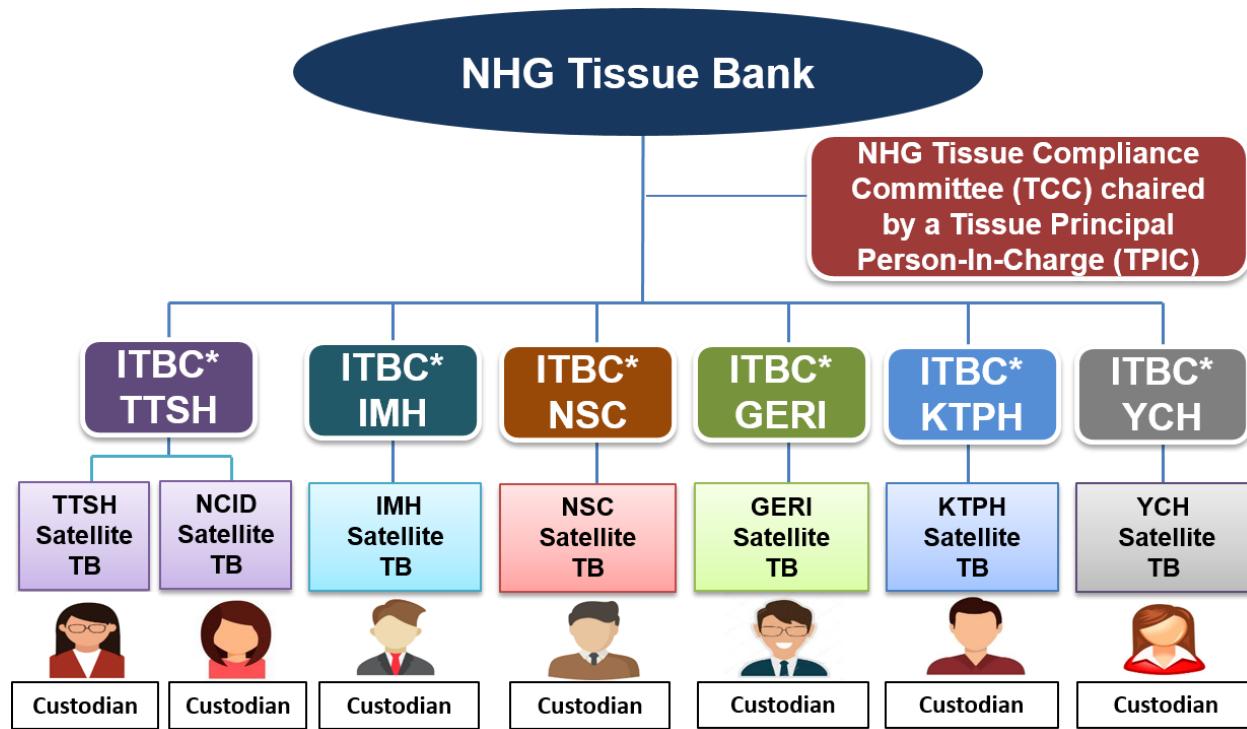
With the activation of the HBRA Human Tissue Framework (HTF) on 01 November 2019, researchers who are collecting, storing, importing, supplying or exporting human tissue would need to do so under the supervision and control of a tissue bank. Some common examples of tissue banking activities that require tissue bank / tissue collection registration include:

- a) Collection of additional tissue on top of what is required for the primary scope of the current research study solely for storage and use in future research (i.e. study not yet approved by an IRB).
- b) Collection of tissue solely for bio-banking (where tissue is not collected for a research study that requires/ had obtained IRB approval).
- c) Storage of leftover tissue from completed studies for use in future research.
- d) Supply of leftover tissue from completed studies to another IRB approved research (HBR or clinical trial) where the researcher is not a PI, Co-I or collaborator.

For NHG researchers, the tissue bank / tissue collection application process is described in **Section 9.2.1 and 9.2.2**. Researchers from non-NHG institutions should check with their respective institution research office on the tissue bank registration process if they are performing any of the above activities.

## 9.2.1 NHG Tissue Governance Structure

Figure 2: NHG Tissue Governance Structure



NHG has adopted a mothership model with multiple satellite tissue banks under its supervision as illustrated in **Figure 2** and has declared itself as one tissue bank to the Ministry of Health (MOH).

### 9.2.1.1 Responsibilities of NHG Tissue Compliance Committee (TCC)

All NHG institutional tissue banks are governed under the oversight of the NHG Tissue Compliance Committee. Responsibilities of the NHG TCC include:

- a. Formulating and maintaining tissue bank policies and SOPs
- b. Reviewing and approving Tissue Bank / Tissue Collection applications
- c. Conducting continuing review of ongoing tissue banks and tissue collection protocols annually
- d. Reviewing non-compliance reports, Serious Adverse Event (SAE) reports, Untoward Occurrence (UO) reports submitted by the Custodian / Tissue Collection Applicant (TCA).
- e. Monitoring Tissue Banking Activities in NHG

### **9.2.1.2 Responsibilities of Tissue Principal Person-In-Charge (TPIC)**

The NHG TCC is chaired by the TPIC. On behalf of the NHG Tissue Bank, the TPIC performs the following functions:

- a. Notifies MOH before the commencement of any tissue banking activity conducted under the supervision of the NHG Tissue Bank
- b. Reports any suspected offence or contravention to the legal provisions set out in the HBRA and its Regulations
- c. Reports any Serious Adverse Event (SAE) resulting from tissue banking activity (intended for human application) conducted under the supervision of the NHG Tissue Bank.
- d. Reports any Untoward Occurrence (UO) resulting from the removal of human tissue conducted under the supervision of the NHG Tissue Bank.
- e. Submits a Declaration of Compliance to MOH annually

### **9.2.1.3 Responsibilities of Institutional Tissue Bank Committee (ITBC)**

The ITBC is an institution-endorsed committee, which comprises clinician(s) practicing in the institution, researcher(s) and Institution Representative for Research (IR). The ITBC endorses tissue bank and tissue collection applications and reviews requests for the utilization of tissue stored in the institution's tissue banks.

Researchers from non-NHG institutions should check with their respective institution research office on the tissue bank governance structure.

## **9.2.2 NHG Tissue Bank / Tissue Collection Application Process**

Researchers from NHG institutions may appoint a tissue bank custodian who bears the overall responsibility for the set up and maintenance of the tissue banks. The NHG custodian / tissue collection applicant (TCA) should download the tissue bank / tissue collection application form(s) from the NHG Research Website (<https://www.research.nhg.com.sg>), complete them, and obtain endorsement from the Department Representative (DR) and Institutional Tissue Bank Committee (ITBC) before submitting the form(s) to the NHG Tissue Compliance Committee (TCC) Secretariat via [NHGTCCSecretariat@nhg.com.sg](mailto:NHGTCCSecretariat@nhg.com.sg). The TCC Secretariat would perform a preliminary review of the applications and route them to the DSRB / TCC for review.

*NHG researchers may access the NHG Institutional Tissue Bank Committee (ITBC) Contact Points at <https://mynhg.nhg.com.sg> > Home > Group Research > Research Compliance Unit > Tissue Banking*

For biobank tissue collections independent from an IRB approved study or researchers who are collecting extra tissue for future research, both the tissue bank application form and the tissue collection application form would need to be completed. The tissue collection application form would be additionally reviewed and acknowledged by the DSRB before it is routed to the TCC for review and approval. This is to ensure that the recruitment and consent process for donors comply with the ethics requirements and the HBRA.

For researchers who intend to store leftover tissue from completed studies for future research that has not been approved by an IRB or intend to supply the leftover tissue to another IRB approved research (HBR or clinical trial) where he/she is not a PI, Co-I or collaborator, only the tissue bank application form would need to be completed. The endorsed tissue bank application form would be routed by the TCC Secretariat to the TCC for approval. DSRB review would not be required in such instances as these completed studies had previously been approved by the IRB and do not involve new tissue collections.

The NHG tissue bank / tissue collection registration process is summarized in **Figure 3**.

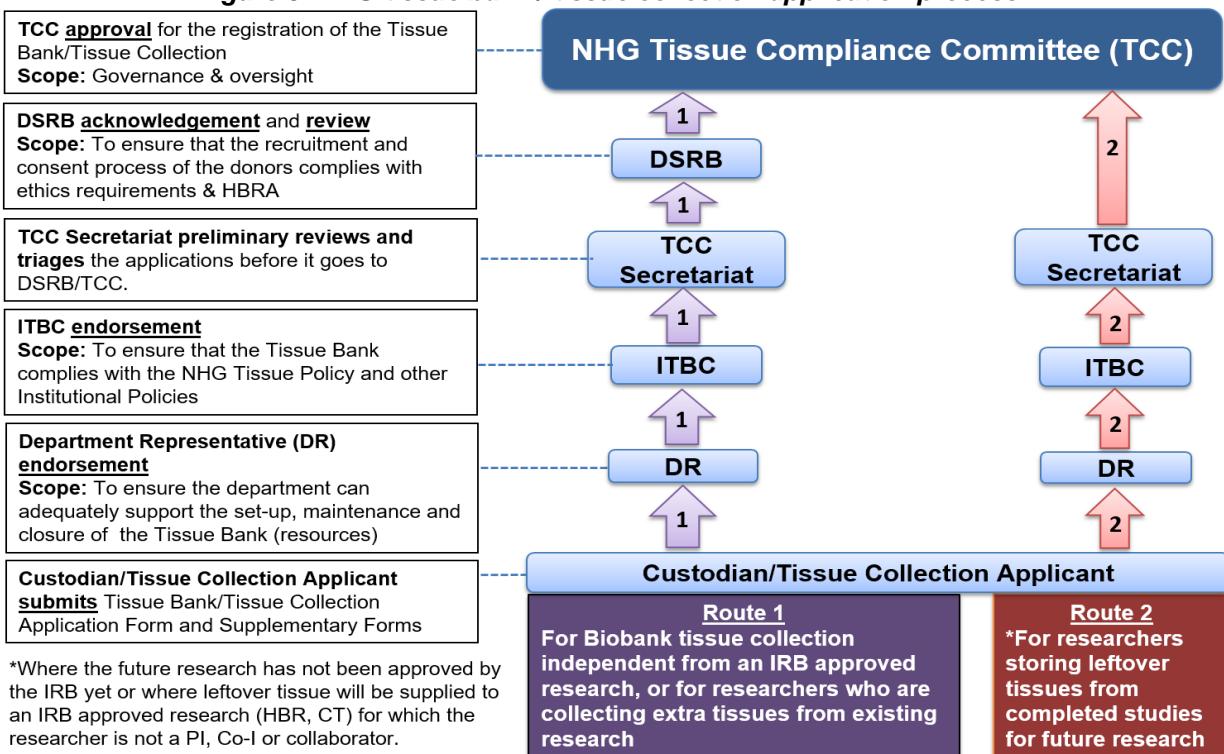


### **Quick Tip**

**Confused over which form to submit? (i.e. tissue bank application form, tissue collection form or both?) The Tissue Bank Application form contains a guide that helps you to determine the correct form to use.**

**\*NOTE: The tissue bank / tissue collection application forms can only be accessed when you have direct access to the NHG Intranet. These documents are strictly for internal circulation among NHG Staff and Authorized personnel only.**

**Figure 3: NHG tissue bank / tissue collection application process.**



### 9.2.3 NHG Tissue Bank / Tissue Collection Endorsement Process for Multi-site Collaborations

#### Tissue banks that straddle across more than one NHG institution

The custodian or TCA from all involved institutions will be required to submit an application to TCC. The application will need to first route to each of the institutions' DRs and ITBCs or equivalent for endorsements. This will allow all institutions to have oversight of the tissue banking activity. A lead tissue bank custodian may be identified to coordinate the applications.

#### Tissue Banks that straddle across NHG and non-NHG institutions and where a NHG institution is the Lead Tissue Bank

Regardless of the site of the tissue bank, the NHG custodian / TCA will be required to submit an application to TCC. The application should be endorsed by the NHG institution(s) DRs, ITBCs and CMBs or equivalent. CMB's acknowledgement is needed given the additional responsibilities that the NHG institution has to undertake as the lead tissue bank.

Tissue Banks that straddle across NHG and non-NHG institutions and where a non-NHG institution is the Lead Tissue Bank

Regardless of the site of the tissue bank, the NHG custodian / TCA will be required to submit an application to TCC. The endorsement of the NHG institution(s) HODs, ITBCs or equivalent are necessary. CMB endorsement is not required.

## **9.3 Key Human Tissue Framework Requirements**

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It is important to ensure that the tissue bank processes and documentation are aligned with the regulatory requirements of the HTF. Key HTF requirements for researchers to take note of include:

- a) Operational requirements for collection, storage, supply, import and export of tissue for research
- b) Consent requirements
- c) Operational requirements for tissue banks that stores or supplies tissues for use in research involving human tissue transplantation

For more information on the HBRA and its regulations, please refer to the Ministry of Health website: <https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act>.

### **9.3.1 Key HTF Requirements for Tissue Banking Activities**

#### **9.3.1.1 Removal and Collection of Human Tissue**

- a) Appropriate consent must be obtained from the donor or donor's legal representative (where applicable) before the removal of tissue.
- b) Human tissue should not be removed from any of the following persons unless the removal of the tissue was primarily for a therapeutic or diagnostic purpose:
  - i) Adult or minor who lacks mental capacity;
  - ii) Minor who lacks sufficient understanding and intelligence to give consent

However, an IRB may waive the above requirement if the board is satisfied that

- i) The removal involves no more than minimal risk to that person; and
- ii) 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.
- c) If the human tissue was removed from a donor for a therapeutic or diagnostic purpose, the tissue should not be stored, supplied or used for research or any other purpose unless the medical practitioner or healthcare institution had completed all necessary therapeutic or diagnostic procedures and no longer require the tissue or part of the tissue for the treatment. The medical practitioner should also document that a formal assessment had been performed to confirm that all therapeutic or diagnostic procedures have been

completed and the leftover tissue is no longer required for the patient's treatment, before it is used for research.

- d) Personnel involved in tissue removal must be qualified and trained to do so.
- e) Appropriate measures must be in place to prevent or control the spread of any communicable disease which is or may be due to the contamination or infection of any tissue.
- f) Instruments and equipment used for the removal of tissue must undergo regular maintenance and subjected to quality controls.
- g) An incidental finding (IF) 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 should be formulated. The policy must be communicated to all donors and recipients of every tissue received by the tissue bank on or after 01 Nov 2019 (HTF activation date). If the policy provides for the donor to be re-identified and informed in the case of an IF, the donors' wishes should be communicated to the recipient as well.

#### **9.3.1.2. Storage of Human Tissue**

- a) Appropriate consent must be obtained from the donor or donor's legal representative (where applicable) for the storage and subsequent use of tissue for future research.
- b) The storage and/or subsequent use is in accordance with any conditions or restrictions specified as part of the appropriate consent
- c) Measures must be in place to protect the confidentiality and maintain the privacy of information relating to the donor of each tissue.

#### **9.3.1.3 Supply of Human Tissue**

- a) Human tissue may be supplied for use in research only after:
  - i) Appropriate consent had been obtained for the tissue to be used in research;
  - ii) The intended use is in accordance with any conditions or restrictions specified as part of the appropriate consent; and
  - iii) The recipient is informed of the requirements referred to in (i) and (ii)

- b) Before supplying individually-identifiable tissue for use in research, the tissue bank must ensure that:
  - i) An institutional review board (IRB) has approved the proposed research that the tissue would be used for; and
  - ii) 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.
- c) Before supplying non-identifiable tissue for use in research, the tissue bank must ensure that:
  - i) An IRB has approved the proposed research that the tissue would be used for or the tissue bank is satisfied that there is scientific merit for the proposed research; and
  - ii) 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.

#### **9.3.1.4 Export of Human Tissue**

- a) Before exporting any individually-identifiable tissue from Singapore, the tissue bank must ensure that:
  - i) Appropriate consent has been obtained from the donor for the export or removal, as the case may be; and
  - ii) 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.
- b) 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.

#### **9.3.1.5 Import of Human 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.

### **9.3.2 Key HTF Requirements for Consent**

For consent involving deceased persons, please refer to Chapter 5.

For consent involving minors and persons lacking mental capacity, please refer to Chapter 6.

#### **9.3.2.1 Requirements for Appropriate Consent**

The requirements for appropriate consent is fulfilled when consent is obtained in:

- a) In writing;
- b) From the tissue donor personally or their legal representatives;
- c) After the information referred to in HBRA section 12(2) has been provided and explained to the tissue donor or the persons authorised to give consent on the donor's behalf; and
- d) In the presence of a prescribed witness

#### **9.3.2.2 Tracking of Consent and Integrity of Records**

A system must be established to ensure:

- a) That every donor's consent in relation to each tissue under the supervision and control of the tissue bank is accurately tracked; and
- b) The integrity of records of the consent and other information relating to the donor.

#### **9.3.2.3. Exemptions for Appropriate Consent**

The requirement for appropriate consent to be obtained from a tissue donor for the storage, supply and use of tissue in research may be exempted if **ALL** the conditions below are met—

- a) The tissue was removed from a human body any time before 1 November 2019;
- b) 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:
  - i) 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;
  - ii) 12(2)(f) the donor's right to withdraw his or her consent and the limitations of such withdrawal; and
  - iii) 12(2)(i) the extent to which donor records will be kept confidential.
- c) The relevant consent was not withdrawn any time before 1 November 2019.

#### **9.3.2.4 Exemptions for Requiring a Prescribed Witness**

The requirement for a witness to be present during appropriate consent from a tissue donor may be exempted in the following 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.

##### **Scenario 3**

The consent for the removal, storage, supply or use of tissue was given by a tissue donor before 01 November 2019.

#### **9.3.3 Key HTF Requirements for Tissue Banks that Support Transplantational Research**

##### **9.3.3.1 Documentation**

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

##### **9.3.3.2 Tracking of Information Relevant to the Safety and Quality of Human Tissue**

Every transplantational tissue bank must establish a system to ensure that the information relevant to the safety and quality of each tissue under its supervision and control is accurately tracked.

##### **9.3.3.3 Additional Requirements Before Tissue is Released, Supplied or Exported**

Before tissue is released, supplied or exported by a transplantational tissue bank:

- a) The principal person in charge must authorize the release, supply or export of the tissue in writing; and

- b) The transplantational tissue bank must ensure that the following information is provided 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

#### **9.3.3.4 Notification by Recipient of Human Tissue**

Every transplantational tissue bank must ensure that the recipient of human tissue stored or supplied by the tissue 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 (SAE). 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.

#### **9.3.3.5 Management of tissue contamination**

Every transplantational 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:

- a) Traceability of tissue;
- b) Traceability of equipment and material used to process the tissue;
- c) Processing and preservation of tissue;
- d) Recall procedure for tissue.

#### **9.3.3.6 Quality and safety management systems**

- a) Every transplantational 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:
  - i) Qualification and training of personnel handling tissue;
  - ii) The method of processing and preservation to retain the biological function compatible with its intended use;
  - iii) Appropriate labelling and storage conditions;
  - iv) Management of quality control and inventory;
  - v) Suitability and testing of tissue donors.

- b) An appropriate and effective system must be established to ensure the recall of tissue which had been unintentionally or otherwise erroneously supplied for use in research involving human tissue transplantation.

## **9.4 Serious Adverse Event / Untoward Occurrence Reporting**

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### **9.4.1 Definitions of SAE and UO**

Serious Adverse Event (SAE) - Any occurrence associated with the procurement, testing, processing, storage or distribution of **human tissue (including gametes or embryos) intended for human application (i.e. human transplantation)** which:

- a) Results in or contributes to death;
- b) Is life-threatening;
- c) Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- d) Results in or contributes to persistent or significant disability or incapacity;
- e) Results in the transmission of a communicable disease; or
- f) Results in any misidentification or mix-up of any type of tissue, gametes or embryo.

Untoward Occurrence (UO) - Any occurrence associated with the **removal of human tissue primarily for research** that:

- a) Results in or contributes to death;
- b) Is life-threatening;
- c) Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- d) Results in or contributes to persistent or significant disability or incapacity;
- e) Results in the transmission of a communicable disease;
- f) Results in any misidentification or mix-up of any type of tissue, gametes or embryo; or
- g) Results in or contributes to a congenital anomaly or birth defect.

### **9.4.2 SAE / UO Assessment**

The custodian / TCA must review the event and assess the causality of the event and the type and severity of harm / potential harm:

- a) Causality – The custodian / TCA should evaluate the causal relationship between SAE / UO and tissue banking activity. The expression ‘reasonable causal relationship’ is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. The following conditions might help to assess causality:
  - (i) The event has a reasonable temporal relationship to the tissue banking activities,
  - (ii) The event could not have been produced by the underlying disease states,
  - (iii) The event could not have been due to other non-tissue bank interventions,
  - (iv) The event follows a known pattern of response to the tissue banking activities, or
  - (v) The event disappears with cessation of tissue banking activities.

- b) Type and severity of harm / potential harm – The custodian / TCA must evaluate the type and severity of harm caused to the safety (e.g. physical hurt is caused) & welfare (e.g. feeling threatened or humiliated, breach of confidentiality or the invasion of privacy, incurring cost without consent of the tissue donor / recipient, affecting one's autonomy) of tissue donors & recipients.

For information on the SAE / UO reporting process, NHG custodians may refer to **Section 9.7.4 SAE / UO Reporting**.

For custodians / TCAs from non-NHG institutions, please check with your research office / relevant institutional authority on the non-compliance / SOC reporting process.

## **9.5 Suspected Offence or Contravention (SOC) Reporting**

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A non-compliance refers to the failure to abide by the approved protocol, the relevant institutional requirements or applicable regulations governing the protection of tissue donors. An SOC refers to any **non-compliance to the legal provisions set out in the HBRA and its Regulations**. Hence, not all non-compliances are SOCs and non-compliances reported by the custodian / TCA would need to be assessed by the RI / TB to determine if it is an SOC reportable to MOH.

For more information on the non-compliances reporting process, NHG custodians may refer to **Section 9.7.3 Non-compliances Reporting**.

For custodians / TCAs from non-NHG institutions, please check with your research office / relevant institutional authority on the non-compliance / SOC reporting process.

### **9.5.1 Assessment of SOCs**

An SOC would be deemed reportable to MOH if it has resulted in harm or had the potential to cause harm to the safety and welfare of tissue donors. The following scenarios are examples of “harm” to the safety and welfare of tissue donors:

- a) Physical hurt is caused
- b) Mental and emotional distress such as feeling threatened or humiliated
- c) Breach of confidentiality or the invasion of privacy
- d) Incurring cost without consent
- e) Affecting one’s autonomy

## **9.6 Cessation of Tissue Bank Operations**

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The custodian must notify the TCC (For NHG custodians) or equivalent (For non-NHG custodians) on the intention to cease operating. For NHG custodians, this is performed by submitting a completed tissue bank status report form to [NHGTCCSecretariat@nhg.com.sg](mailto:NHGTCCSecretariat@nhg.com.sg).\* The TPIC or designee will notify the Director of MOH in the applicable form set out at the relevant website as soon as possible and in any event 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 details of the receiving tissue 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) Any other information as required by the Director of MOH

**\*NOTE: For non-NHG custodians, please check with your relevant institutional authority / research office on the notification process for cessation of tissue banks.**

### **9.6.1 Preparation for Tissue Bank Closure**

In preparation for the closure of a tissue bank, the custodian and/or designee must ensure the following (but not limited to) are performed or resolved:

- a) All data queries received to date have been resolved to the fullest extent possible.
- b) All reportable events (e.g. Serious Adverse Events (SAEs), untoward occurrences (UOs), non-compliances) have been submitted to the TCC or equivalent and sponsor (if applicable).
- c) All essential documents (e.g. original signed informed consent forms, data collection forms) are filed in the tissue bank file and databases are complete and available for transfer or archiving.
- d) Any unused tissue bank supplies and/or equipment are destroyed or returned to sponsor (if applicable).
- e) Tissue samples are reconciled and tissue specimen logs are up to date.
- f) Where applicable, ensure a Material Transfer Agreement of equivalent is established before transferring the entire tissue collection to another tissue bank or a new custodian.

- g) Where applicable, ensure that the transfer or tissue samples and tissue bank documents to another tissue bank or a new custodian is carried out in accordance to the HBRA requirements.
- h) All used and unused tissue samples are disposed in accordance to institutional guidelines / SOPs if they are to be destroyed.
- i) Upon closure of the tissue bank, if the custodian needs to keep the data for future research use, the custodian should follow institutional and regulatory requirements for retaining the tissue bank data.

## **9.7 Submissions to the NHG Tissue Compliance Committee (TCC)**

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**IMPORTANT: Section 9.7 is only applicable to custodians from NHG Institutions. For custodians from non-NHG institutions, please check with your research office / relevant institutional authority on the required submission and their respective processes and timelines.**

In addition to the initial registration of tissue banks and tissue collections (Refer to **Section 9.3**) tissue custodians / tissue collection applicants from NHG institutions would also be required to perform the following submissions to the TCC.

- a) Tissue Bank / Tissue Collection Amendments
- b) Continuing Review
- c) Non-Compliances Reporting
- d) SAE / UO Reporting

The relevant forms for the above submissions can be downloaded from <https://mynhg.nhg.com.sg> > Home > Group Research > Research Compliance Unit > Tissue Banking > Forms and Templates. These documents are strictly for internal circulation among NHG Staff and Authorized personnel only.

### **9.7.1 Tissue Bank / Tissue Collection Amendments**

No deviation from, or changes of the tissue banking activities should be implemented without documented approval from the TCC, except where necessary to eliminate apparent immediate hazard(s) to the donors, or when the change(s) involves only logistical or administrative aspects of the tissue bank (e.g. change of telephone number).

Any deviation from, or a change of, the protocol to eliminate an immediate hazard should be promptly reported to the TCC as soon as possible but not later than 7 calendar days upon first knowledge by the custodian / tissue collection applicant. For more information, please refer to **Section 9.7.3 Non-Compliances Reporting**.

For tissue bank / tissue collection amendments, the following must be submitted

- i. Tissue Bank Amendment / Tissue Collection Amendment Form
- ii. Any amended documents
- iii. Any other relevant documentation when, in the judgment of the TCC or the IRB, the additional information would add meaningfully to the protection of the rights, safety and wellbeing of the tissue donors
- iv. Any other documentation that the TCC may specifically request

## **9.7.2 Continuing Review**

The TCC will conduct continuing review of ongoing tissue banks and tissue collection protocols once per year. Continuing TCC review is required as long as tissues are stored in the tissue bank.

Approvals for Tissue Banks / Tissue Collections expire on 28 February each year. Custodians are strongly advised to submit a duly completed Tissue Bank Status Report Form and/or Tissue Collection Status Report Form to the TCC at [NHGTCCSecretariat@nhg.com.sg](mailto:NHGTCCSecretariat@nhg.com.sg) between 01 January to 31 January to allow sufficient time for the TCC to process the application prior to Tissue Banks/ Tissue Collections approval expiry. The information provided in the status report form should cover for the period between 01 January to 31 December of the preceding year.

Tissue Banks or Tissue Collections that were reviewed by the full Quorum and determined to require a higher frequency of continuing reviews at shorter intervals due to the high degree of risks involved must additionally submit their status report forms at the intervals set on by the Quorum.

The custodian / TCA is responsible for submitting the status reports for continuing review before the expiration date and in ample time for the TCC review. If the custodian / TCA fails to submit the status reports for an active Tissue Bank / Tissue Collection, or if the TCC has not reviewed and approved the submitted status reports by the expiration date, the Tissue Bank / Tissue Collection will be considered lapsed and all tissue banking activities will be required to cease immediately.

If tissue banking activities were performed during the lapse of TCC approval, the custodian / TCA will be required to submit a non-compliance report to the TCC by using a Tissue Non-Compliance/ Protocol Deviation Report Form to document activities that were conducted during the lapse.

### **9.7.2.1 Supporting Documents for Continuing Review**

The custodians / TCAs applying for renewal of approval of a tissue bank / tissue collection must provide the following information to the TCC (where applicable):

#### **Tissue Bank Status Report**

- a) SAEs/ UOs since last review;
- b) Non-compliances/ deviation reports since last review;
- c) Tissue Bank protocol amendments since last review;
- d) Potential conflicts of interest since the last review;
- e) Any other relevant information, especially information about compliance adherence associated with the Tissue Bank.

### Tissue Collection Status Report

- a) Donor recruitment;
- b) Number and reasons for withdrawal of donors;
- c) SAEs/ UOs since last review;
- d) Non-compliances/ deviation reports since last review;
- e) Tissue Collection protocol amendments since last review;
- f) Complaints about the tissue collection and related activities;
- g) Any other relevant information, especially information about the risks associated with the tissue collection.

### **9.7.2.2 Tissue Bank / Tissue Collection Status Reporting**

The custodian or TCA must also indicate the status of the tissue bank and tissue collection, where applicable, details of each as follows:

#### Status of Tissue Bank

- a) Ongoing. No new tissue to be added (maintenance of existing tissues only).
- b) Ongoing. New tissues may be added from DSRB-approved studies/ DSRB-acknowledged tissue banks.
- c) Ongoing. New tissues may be added from TCC-approved Tissue Collections.
- d) Suspended
- e) Terminated
- f) Closed

#### Status of Tissue Collection

- a) Ongoing (Recruitment of new donors ongoing)
- b) Ongoing (Recruitment closed, enrolled donors on follow up either for ongoing tissue collection or data collection)
- c) Not yet initiated (Pre-screening and recruitment process not started yet)
- d) Suspended
- e) Terminated
- f) Completed
  - (i) The Tissue Collection is permanently closed to the recruitment of new donors
  - (ii) All enrolled donors have completed their tissue donation
  - (iii) Collection data for all enrolled donors has been completed

### **9.7.3 Non-Compliances Reporting**

### **9.7.3.1 Definition of Non-Compliance**

Non-compliance is a failure to abide by the approved protocol, the policies and procedures of the TCC, the relevant institutional requirements, or applicable regulations governing the protection of tissue donors. Some examples of non-compliance include failure to (but are not limited to):

- a) Obtain approval for operating a Tissue Bank/initiating tissue collection
- b) Obtain renewal of approval for a Tissue Bank/Tissue Collection Protocol,
- c) Obtain appropriate informed consent when required,
- d) File a SAE/UO report,
- e) Submit amendment(s) for review and approval,
- f) Adhere to the approved protocol,
- g) Adhere to the regulations, policies, and procedures related to tissue banking activities.

### **9.7.3.2 Non-Compliance Assessment**

The custodian / TCA must review the non-compliance and assess whether the event arises in relation to tissue banking activities conducted under the supervision and control of the tissue bank or tissue collection. The custodian / TCA must also assess the type and severity of harm / potential harm caused to the safety (e.g. physical hurt is caused) & welfare (e.g. feeling threatened or humiliated, breach of confidentiality or the invasion of privacy, incurring cost without consent of the tissue donor/ recipient, affecting one's autonomy) of tissue donors & recipients.

### **9.7.3.3 Non-Compliance Reporting Process**

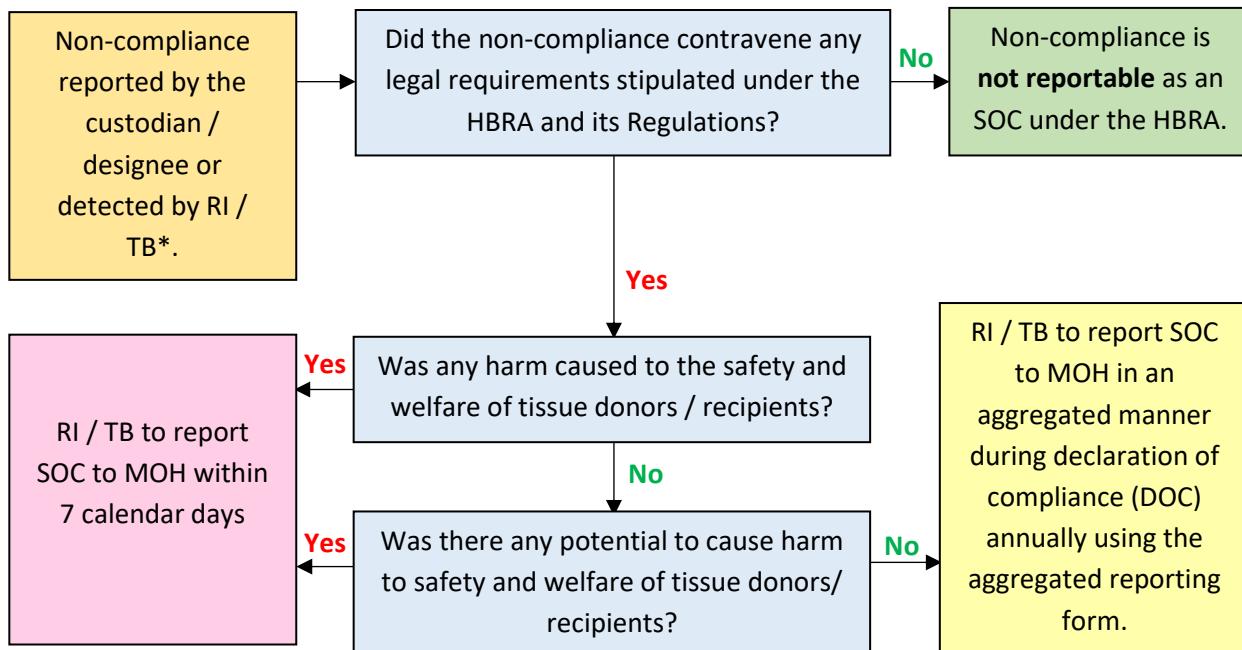
The custodian / TCA must report any non-compliances to the TCC by submitting a completed Tissue Non-Compliance/ Protocol Deviation Report Form to [NHGTCCSecretariat@nhg.com.sg](mailto:NHGTCCSecretariat@nhg.com.sg).

### **9.7.3.4 Non-Compliance Reporting Timelines**

- a) The custodian / TCA or designee must report any non-compliance to the TCC as soon as possible but not later than 7 calendar days after first knowledge by the custodian / TCA.
- b) If the non-compliance was assessed to contravene any of the legal requirements stipulated under the HBRA and its Regulations and had caused harm or had the potential to cause harm to the safety and welfare of tissue donors, the TPIC or designee would need to submit the information to the Director of MOH in the applicable form set out at the relevant website as soon as possible and in any event not later than 7 calendar days after the tissue bank or TPIC

or designee first becomes aware of the information. Refer to **Figure 4** for the workflow on assessing and reporting Suspected Offence and Contravention (SOC)

**Figure 4 Workflow for assessing and reporting SOC**



**\*Note:** The RI / TB refers to the relevant institutional authority that governs all institutional tissue banks. For NHG institutions, this refers to the NHG Tissue Compliance Committee (TCC).

Please refer to **Section 9.5 Suspected Offence or Contravention (SOC) Reporting** for more information.

## **9.7.4 SAE / UO Reporting Process**

The NHG custodian / TCA or designee is responsible for the timely reporting of any SAE / UO to the TCC by submitting a completed SAE / UO Report Form to [NHGTCCSecretariat@nhg.com.sg](mailto:NHGTCCSecretariat@nhg.com.sg). The Tissue Principal Person In Charge (TPIC) or designee will review and submit the information to the Director of MOH, if necessary.

### **9.7.4.1 SAE / UO Reporting Timelines**

#### a) Results in death or is life-threatening

- (i) NHG custodians / TCAs must submit all recorded information on the SAE / UO to the TCC **immediately after first knowledge** by the custodian, and any additional relevant information should be reported to the TCC **as soon as possible** after the record is made.
- (ii) The TPIC or designee will review and submit the information to the Director of MOH in the applicable form set out at the relevant website as soon as possible and in any event not later than **7 calendar days** after the tissue bank or the TPIC or designee first becomes aware of the event, whichever is the earlier; and any additional relevant information about the SAE is recorded and submitted to the Director of MOH **within 8 days** after the record is made.

#### b) Does not result in death and is not life-threatening

- (i) NHG custodians / TCAs must submit all recorded information on the SAE / UO to the TCC **immediately** after first knowledge by the custodian, and any additional relevant information should be reported to the TCC **as soon as possible** after the record is made.
- (ii) The TPIC or designee will review and submit the information to the Director of MOH in the applicable form set out at the relevant website as soon as possible and in any event not later than **15 calendar days** after the tissue bank or the TPIC or designee first becomes aware of the event, whichever is the earlier.

The SAE / UO reporting requirements are summarized in **Table 1**.

**Table 1: Summary of SAE / UO reporting requirements**

	SAE / UO resulting in death or is life-threatening	SAE / UO which does not result in death and is not life-threatening
<b>Timeline for Initial Report to TCC</b>	Immediately after first knowledge by the custodian	
<b>Timeline for Follow-Up Report to TCC</b>	As soon as possible after the initial report	
<b>Timeline for Initial Report to MOH</b>	As soon as possible but not later than 7 calendar days after the tissue bank or the TPIC or designee first becomes aware of the event	As soon as possible but not later than 15 calendar days after the tissue bank or the TPIC or designee first becomes aware of the event
<b>Timeline for Follow-Up Report to MOH</b>	Within 8 days after the initial report	-

## **9.8 Tissue Bank Essential Documents**

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The custodian / TCA should maintain a tissue bank file containing essential documents. The purpose of maintaining essential documents is to keep an audit trail on the management of human tissue from its collection, processing, storage, supply and destruction (where applicable). Essential documents would also allow the monitors, auditors and inspectors to confirm the compliance of tissue banking activities with the applicable regulatory requirements and institutional policies and SOPs.

Essential documents may be grouped into the various categories. The essential documents in these categories include (but are not limited to) the following:

- b) Tissue Compliance Committee (TCC) or equivalent (For Non-NHG institutions) documents
  - i. Approval letters
  - ii. Initial application forms and documents submitted and approved by the TCC or equivalent
  - iii. Amended application forms, amendment cover note or amendment summary
  - iv. TCC or equivalent approved amended documents
  - v. Annual Tissue Bank Status Report Forms
  - vi. Serious Adverse Event (SAE), Untoward Occurrence (UO) and Non Compliance reports
- c) Tissue Bank Team
  - i. Contact details of tissue bank staff
  - ii. Tissue Bank Responsibility / Delegation log
  - iii. Curriculum Vitae (CV) of all tissue bank team members
  - iv. Copy of training certification for all tissue bank team members
  - v. Training documentation (e.g. training record form(s), training slides)
- d) Laboratory
  - i. Specimen collection/ processing/ request/ retrieval/ destruction records
  - ii. Specimen procurement records
  - iii. Specimen Inventory logs
  - iv. Shipping records (e.g. courier shipment receipts, shipment tracking log)
  - v. Equipment maintenance records (e.g. calibration certificates)
  - vi. Temperature logs
- e) Other documents
  - i. Donor Screening / Enrolment / Identification logs
  - ii. Signed informed consent forms
  - iii. Monitoring documents (e.g. monitoring reports)
  - iv. Significant correspondences

v. Tissue bank collaboration agreement (e.g. Material Transfer Agreement)

NHG researchers may refer to the PCT 1501-01 Tissue Bank File Contents Template on the NHG Research Website (<https://www.research.nhg.com.sg>) for a full list of essential documents to be maintained in the tissue bank file. The essential document templates, logs and forms can also be downloaded from the NHG Research Website\*.

**\*NOTE: These document downloads can only be accessed when you have direct access to the NHG Intranet. These documents are strictly for internal circulation among NHG Staff and Authorized personnel only.**