INVESTIGATOR'S MANUAL

3rd EDITION

FOR DSRB BIOMEDICAL DOMAINS

National Healthcare Group

Adding years of healthy life

3rd Edition: October 2017

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 (as of Nov 2017)

Affiliated Institutions

- National University Health System
  - National University Hospital
  - Yong Loo Lin School of Medicine, NUS
  - Saw Swee Hock School of Public Health, NUS
  - Faculty of Dentistry, NUS
  - Alice Lee Centre for Nursing Studies, NUS

Non-Affiliated Institutions (Partners)

- Agency for Integrated Care
- Ang Mo Kio Thye Hua Kwan Hospital
- Dover Park Hospice
- Health Sciences Authority
- Health Promotion Board
- Jurong Health Services
  - Ng Teng Fong Hospital
  - Jurong Medical Centre
  - Jurong Community Hospital
- Lilly-NUS Centre for Clinical Pharmacology
- Singapore Institute for Clinical Sciences, A*STAR

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 2017 (as of November), this figure stands at 1008 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 627 in 2017. 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 Singapore Guideline for Good Clinical Practice (1998) 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 launch of the Third 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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National Healthcare Group
Deputy Chairman Medical Board,
Divisional Chairman, Integrative & Community Care
Director, Institute of Geriatrics & Active Ageing
Specialist in Geriatric Medicine & Senior Consultant, Dept of Continuing & Community Care
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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 plan
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
RDO	NHG Research and Development Office
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)

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 4 divisions:

DSRB Operations & Management	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.
Research Quality Management (RQM)	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.
Research Education (RE)	RE develops training programmes and resources, as well as conducts educational support initiatives for investigators and researchers. RE also oversees the propagation of a Responsible Conduct of Research (RCR) culture and promotes RCR awareness within the research community.
Partnerships & Outreach (P&O)	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.

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

The DSRB is an independent committee constituted by medical, scientific and non-scientific members, 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. 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.

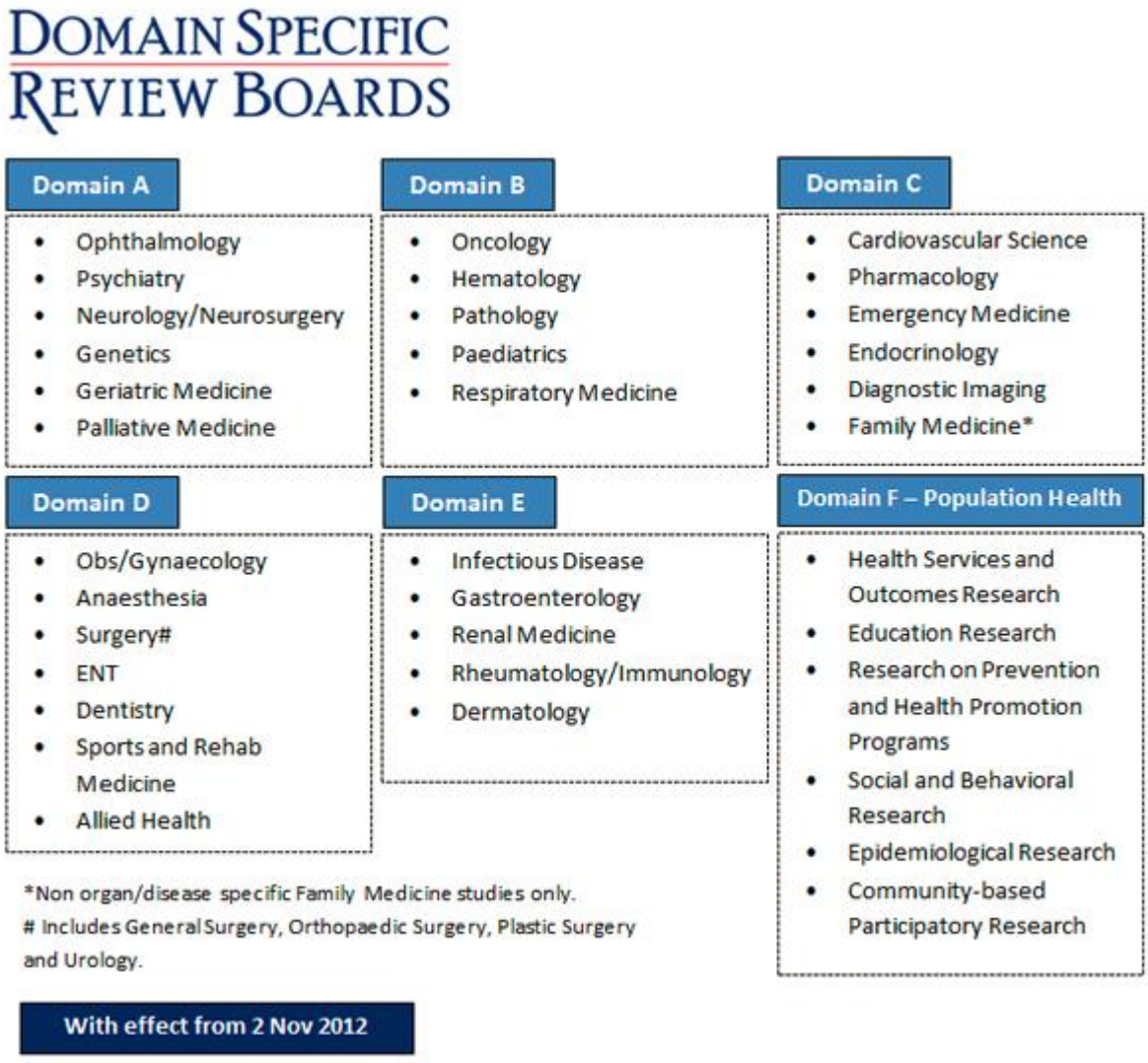
Other officials of institutions which conduct research under the oversight of NHG DSRB, may not override the decision of DSRB (or REC, where applicable). The REC is a committee comprising the DSRB chairpersons and laypersons, which collectively establishes and oversees the policies and implementation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

There are currently five biomedical domains (A-E) that are based on broad but related disease groupings and a sixth 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



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

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 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:
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:
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

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 (i.e. chemical drugs and biologics);

b. Medicines Act and its subsidiary legislation – applicable for clinical trials of medicinal products (i.e. cell, tissue and gene therapy products, complementary health products);

c. Human Biomedical Research Act and its subsidiary legislation – 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 June 2015);

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" means 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. ICH GCP

CLINICAL TRIAL / STUDY – 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. The terms clinical trial and clinical study are synonymous.

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

III. US DHHS Regulations

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

HUMAN SUBJECT means a living individual about whom an investigator (whether professional or student) conducting research obtains

a. Data through intervention or interaction with the individual, or

b. Identifiable private information.

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.

IV. US FDA Regulations

CLINICAL INVESTIGATION is any experiment that involves a test article and one or more human subjects 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 subject 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.

V. BAC Report on Ethics Guidelines for Human Biomedical Research (Published June 2015)

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 or indirectly through the use of their biological materials 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. Ministry of Health Singapore Code of Ethical Practice in Human Biomedical Research (published April 2009);

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.

c. Justice – requires that the benefits and burdens of research be distributed fairly, e.g. the need to have a reasonable inclusion and exclusion criteria.

II. MOH Code of Ethical Practice in Human Biomedical Research (April 2009)

The credibility of human biomedical research with society is dependent upon the maintenance of the highest ethical standards in its conduct. Research is ethically justifiable only if it is scientifically sound and does not expose research subjects to unwarranted discomfort or risks without likely benefit to the advancement of biomedical science. Research should also abide by accepted moral standards within the community and be carried out responsibly, in ways that respect and protect the research subjects, and maintain scientific integrity to promote trust and accountability.

Researchers have a personal and non-delegable responsibility to ensure the ethical conduct of their research. This Code lays down principles and standards for ethical practice in human biomedical research in Singapore. Researchers should use this Code as a yardstick for their conduct and behaviour. In addition, researchers should have an understanding of research ethics, develop the knowledge, skills and attitude needed to manage ethical conflicts, and to consult with colleagues, ethics committees and other experts when ethical issues arise.

Researchers are to uphold the principles fundamental to the protection of human subjects. In general, researchers are expected to:

a. Respect persons as individuals:

   i. Obtain fully informed consent from subjects who are autonomous;

   ii. Accord due protection to persons with diminished autonomy and who are vulnerable;

   iii. Protect privacy and maintain data confidentiality at all times;

b. Strive to promote the well-being and safety of human research subjects, protecting them from unnecessary risks, and never let the goals of research undermine this priority;

c. Abide by local laws, regulations, guidelines and commonly agreed standards of good practice on the conduct of human biomedical research;

d. Embody professionalism by upholding integrity, openness, and a commitment to intellectual honesty in the conduct of research, and avoid any actual, potential or apparent conflict of interest;

e. Exercise responsible custodianship of resources under their charge and be a responsible steward in the use and management of those resources;

f. Treat all fellow researchers with dignity and respect, and managing researchers under their supervision with care;

g. Observe the Code in all respects of their professional lives.

1.5 Does My Study Require DSRB Approval?

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 are often created and maintained for purposes that are totally unrelated to research. However, if a database is created with the intention of using the stored data for future research, the creation of such a database will require DSRB review and approval. Individual research projects extracting data from such databases will also require DSRB review and approval.

*TISSUE REPOSITORIES – Operation of human tissue repositories and its data management centre are subjected to oversight by the DSRB. The DSRB will review and approve protocols specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The DSRB will also review and approve a sample collection protocol and consent document.

**More information on standing databases (chapter 8) and tissue repositories (chapter 9) will be provided at a later date. For the latest announcements and updates, please refer to the NHG Research Website.*

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 generalisable 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 one or more questions from the checklist is "Yes", the QA / QI study will be subject to DSRB review.			
S/N	**Questions**	**Yes**	**No**
1.	Is the implied consent from subjects inadequate and / or is the activity inconsistent with subject's privacy and confidentiality issues?		
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 or outside the usual permissible quality assurance activities?		
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 or the use of a control group or a placebo?		
8.	Does the proposed quality assurance activity seek to gather information about the participant beyond that collected in routine clinical care?		
9.	Does the proposed quality assurance activity potentially infringe the rights, privacy or professional reputation of careers, health care providers or institutions?		

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 studies 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.

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

a. Singapore Statutes Online, available at http://statutes.agc.gov.sg/aol/home.w3p

b. ICH GCP E6(R2) guidelines, available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

c. US Code of Federal Regulations, available at http://www.ecfr.gov/cgi-bin/ECFR?page=browse

d. Belmont Report, available at https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/

e. Declaration of Helsinki, available at http://www.wma.net/en/30publications/10policies/b3/

f. Bioethics Advisory Committee reports, available at http://www.bioethics-singapore.org/index.html

g. Ministry of Health Code of Ethical Practice in Human Biomedical Research, available at http://www.moh.gov.sg

h. NHG Research Online Administration and Management Guidebooks on various DSRB-related topics, available at:
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 → Resources → Proper Conduct of Research SOP & Templates

CHAPTER 2
REGULATORY REQUIREMENTS

2.1 The Human Biomedical Research Act (HBRA)

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. 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.

The key entities in The HBR framework are:

- The Research Institution (RI);
- The Institutional Review Board (IRB); and
- The researcher.

They function together in an interlocking system of 'self-accountability'. Their respective roles and responsibilities are described below.

The 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.

The 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.

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 subjects he enrols 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.

II. 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.

2.1.2 The Human Tissue Framework

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.

Scope and Definitions

Human tissue refers to any human biological material but exclude human biological material specified in the First Schedule. 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.

2.1.3 References and Further Reading

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

- *Singapore Statutes Online, available at http://statutes.agc.gov.sg/aol/home.w3p*
- *Ministry of Health Singapore, Human Biomedical Research Act, available at https://www.moh.gov.sg/content/moh_web/home/legislation/legislation_and_guidelines/human-biomedical-research-act.html*

2.2 The Regulation of Clinical Trials and Clinical Research Materials

2.2.1 The Health Products Act

The Health Products Act is an Act to regulate 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; and
- Therapeutic products (more commonly known as chemical and biologic drugs).

Definitions

CLINICAL TRIAL refers to an investigation (of a therapeutic 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.

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;

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.

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. A whole cell or micro-organism, such as a whole virus or bacterium used as a vaccine;

        B. A part of a micro-organism, such as a sub-unit vaccine;

        C. A plasma-derived product;

        D. A biotechnology-derived substance, such as a protein or polypeptide;

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. Any product containing human or animal cell or tissue;

    iii. Any substance administered to humans with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

    iv. Whole blood or any blood component;

    v. Any Chinese proprietary medicine;

    vi. Any homoeopathic medicine;

    vii. Any medicated oil or balm;

    viii. Any quasi-medicinal product;

    ix. Any traditional medicine.

I. Clinical Trials of Therapeutic Products

Clinical trials of therapeutic products (i.e. "drug trials") are regulated under the Health Products (Clinical Trials) Regulations. To conduct clinical trials of therapeutic products 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: ▪ Locally unregistered therapeutic products. ▪ Locally registered therapeutic products not used in accordance with product registration*. ▪ Healthy volunteers (unless approved population is healthy individuals, e.g. vaccines). **Used for a different indication, patient population, dosing regimen, dosage form, etc. from the approved label.*	For clinical trials involving: ▪ Locally registered therapeutic products used in accordance with product registration.

Table 3: Key differences between CTA and CTN applications

	Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)
Risk level of clinical trial	"Higher risk" trials	"Lower risk" trials
DSRB and HSA submission timelines	Applications to HSA and DSRB may be submitted concurrently	Applications to HSA can only be submitted after obtaining DSRB approval
HSA review timeline	30 working days	5 working days

II. Clinical Trials of Medical Devices

Although the sale and supply of medical devices are regulated under the Health Products Act, clinical trials of medical devices are not regulated by HSA.

Nonetheless, general regulatory controls apply to the use of medical devices in clinical trials.

For more information on these regulatory controls, please refer to the Health Products (Medical Devices) Regulations at http://statutes.agc.gov.sg.

2.2.2 The Medicines Act

The Medicines Act is an Act to make provisions with respect to medicinal products and medical advertisements and matters connected therewith; and to make consequential amendments to the Poisons Act. This Act is also administered by HSA. The regulatory controls in the Medicines Act apply to the following medicinal products:

- Cell, tissue and gene therapy products;

- Complementary health products, which include Chinese proprietary medicines, other traditional medicines, homoeopathic medicines and health supplements.

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.

I. Clinical Trials of Medicinal Products

Clinical trials of medicinal products are regulated under the Medicines (Clinical Trials) Regulations. These include clinical trials investigating:

- Cell, tissue and gene therapy products;

- Complementary health products – which include Chinese proprietary medicines, other traditional medicines, homoeopathic medicines and health supplements.

To conduct clinical trials of medicinal products in Singapore, a CTC from HSA will be required.

Table 4: Characteristics of CTC Applications

Clinical Trial Certificate (CTC) Applications	
Registration status of medicinal product(s)	All clinical trials investigating medicinal product(s) will require a CTC, regardless of the local registration status of the medicinal product(s).
Risk level of clinical trial	All risk levels
DSRB and HSA submission timelines	Applications to HSA and DSRB may be submitted concurrently.
HSA review timeline	60 working days for cell and tissue therapy products 30 working days for all other types of medicinal products

2.2.3 Observational Clinical Trials

OBSERVATIONAL TRIAL is a clinical trial of registered therapeutic products, or clinical trial of licensed medicinal products, where all of the following conditions are met in respect of each product:

a. The product is prescribed by a qualified practitioner to a patient in the usual manner in accordance with the terms of the product registration;

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 qualified practitioner carrying out the trial.

Observational trials are excluded from the regulatory controls under the Health Products Act and Medicines Act.

2.2.4 Clinical Research Materials (CRM)

CLINICAL RESEARCH MATERIALS refer to:

- Any registered or unregistered therapeutic product; or

- Any licensed or unlicensed medicinal product; or
- Any registered or unregistered medical device; or
- Placebo;

That is manufactured, imported or supplied for the purpose of being used in any clinical research* in accordance with a research protocol.

**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.*

Table 5: Applicable regulations for CRM

Clinical Research Material	**Applicable Regulations**
Therapeutic products	Health Products (Therapeutic Products as Clinical Research Materials) Regulations
Medicinal products	Medicines (Medicinal Products as Clinical Research Materials) Regulations
Medical devices	Relevant provisions under the Health Products (Medical Devices) Regulations, incorporating the Health Products (Medical Devices) (Amendment) Regulations 2016

I. CRM Notification to HSA

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

- Import of any CRM.
- Supply of any locally manufactured CRM by the manufacturer.

II. Duties and Obligations of CRM Dealers

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

Table 6: Duties and obligations for supplying and handling of therapeutic products and / or medicinal products

Duties and Obligations	Parties			
	Manufacturer	**Importer**	**Supplier***	**Sponsor**
All CRM				
Maintain records of receipt and supply	√	√	√	√
Ensure compliance with labeling requirements	√	√	√	√
Report unexpected serious adverse drug reactions (USADR) to HSA	-	-	-	√
Notify HSA before recall of CRM	√	√	√	√
Additional requirements for locally manufactured or imported CRM				
Ensure appropriate quality of CRM	√	√	-	-
Maintain records of manufacture	√	-	-	-
CRM supply / use only for clinical research purposes	√	√	√	√
Ensure disposal / export of CRM after research ends	-	-	-	√
Maintain records of disposal / export of CRM	-	-	-	√

**Supplier includes local manufacturer, importer, wholesaler, sponsor and investigator, if the party is involved in the activity of supplying a therapeutic product or medicinal product as a CRM.*

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

Table 7: Duties and obligations for supplying and handling of medical devices

Duties and Obligations	Parties			
	Manufacturer	**Importer**	**Supplier***	**Sponsor**
All CRM				
Ensure appropriate quality of CRM	√	√	-	-
Maintain records of manufacture	√	-	-	-
Maintain records of receipt and supply	√	√	√	√
Ensure compliance with labeling requirements	√	√	√	√
Report medical device defects and adverse effects to HSA	√	√	√	√
Maintain records of complaints	√	√	√	√
Notify HSA concerning field safety corrective actions	√	√	√	√
Notify HSA before recall of CRM	√	√	√	√
Additional requirements for locally manufactured or imported CRM				
CRM supply / use only for clinical research purposes	√	√	√	√
Ensure disposal / export of CRM after research ends	-	-	-	√
Maintain records of disposal / export of CRM	-	-	-	√

**Supplier includes local manufacturer, importer, wholesaler, sponsor and investigator, if the party is involved in the activity of supplying a therapeutic product or medicinal product as a CRM.*

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 therapeutic products and medicinal products must comply with the following requirements.

Table 8: Requirements for record-keeping for therapeutic products (TP) and medicinal products (MP)

	Type of Records		
	Manufacture	**Receipt and/or Supply**	**Disposal (Including Export or Putting to Other Use)**
Applies to	Locally-manufactured CRM	All CRM	Imported or locally manufactured CRM
Party Responsible	Manufacturer	Any person who supplies CRM, including the local manufacturer, importer, wholesaler, sponsor and/or investigator.	Sponsor
Required Elements in Records	-	• Proprietary name (brand name) or other description • Identification number of the CRM (batch no, lot no) • Details of receipt, supply, putting to other use, disposal or export: – Date of receipt, supply, putting to other use, disposal or export; – Quantity of CRM received, supplied, put to other use, disposed, exported; – Name and address of person the CRM was received from, supplied to, or of the person responsible for putting to other use, disposal or export of CRM.	

Duration of Record-Keeping	• 1 year after CRM expiry date, or • 5 years after date of manufacture, assembly and testing (Whichever is longer)	TP or MP used in regulated clinical trial: • No more pending or planned applications for TP / MP registration • 2 years after the last of such registrations have been granted • 2 years after informing HSA of termination of the clinical trial • 6 years after completion of clinical trial (Whichever is the latest) TP or MP in other clinical research studies: 2 years after the supply, putting to other use, disposal or export.

Record-keeping for medical devices must comply with the following requirements.

Table 9: Requirements for record-keeping for medical devices (MD)

	Type of Records		
	Manufacture	**Receipt and/or Supply**	**Disposal (Including Export or Putting to Other Use)**
Applies to	Locally-manufactured CRM	All CRM	Imported or locally manufactured CRM
Party Responsible	Manufacturer	Any person who supplies CRM, including the local manufacturer, importer, wholesaler, sponsor and/or investigator.	Sponsor

Required Elements in Records	-	• Proprietary name (brand name) or other description of the CRM • Identification number or mark of the CRM (batch no, serial no) • Details of receipt, supply, putting to other use, disposal or export: – Date of receipt, supply, putting to other use, disposal or export; – Quantity of CRM received, supplied, put to other use, disposed, exported; – Name and address of person the CRM was received from, supplied to, or of the person responsible for putting to other use, disposal or export of CRM
Duration of Record-Keeping	• Projected useful life of the MD; or • 2 years after the MD is supplied (Whichever is longer)	Unregistered MD used in regulated TP / MP clinical trial: • No more pending or planned applications for TP / MP registration • 2 years after the last of such registrations have been granted • 2 years after informing HSA of termination of the clinical trial • 6 years after completion of clinical trial (Whichever is the latest) Registered MD used in regulated clinical trial, or any MD used in clinical research studies: • Projected useful life of the MD; or • 2 years after the supply, putting to other use, disposal or export (Whichever is longer)

2.2.5 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 http://statutes.agc.gov.sg/aol/home.w3p*
- *Health Sciences Authority website, available at http://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. name, age, address, telephone number, occupation, 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 Nine Data Protection Obligations under PDPA

1. Consent obligation

- To collect, use or disclose personal data only for purposes for which an individual has given his or her consent.

- To allow individuals to withdraw consent, with reasonable notice, and inform them of the likely consequences of withdrawal. Upon withdrawal of consent to the collection, use or disclosure for any purpose, the organisation must cease such collection, use or disclosure of the personal data, unless such collection, use or disclosure without the consent of the individual is required or authorised under PDPA or other written law.

2. Purpose limitation obligation

- An organisation 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.

3. Notification obligation

- To notify individuals of the purposes if there is an intention to collect, use or disclose their personal data on or before such collection, use or disclosure of personal data.

4. Access and correction obligation

Upon request, the personal data of an individual and information about the ways in which his or her personal data has been or may have been used or disclosed within a year before the request should be provided.

- Organisations are also required to correct any error or omission in an individual's personal data upon his or her request.

- Unless the organisation is satisfied on reasonable grounds that the correction should not be made, the organisation should correct the personal data as soon as practicable and send the corrected data to other organisations to which the personal data was disclosed within a year before the correction is made (or, with the individual's consent, only to selected organisations).

5. Accuracy obligation

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

6. Protection obligation

- To make reasonable security arrangements to protect the personal data that the organisation possesses or controls to prevent unauthorised access, collection, use, disclosure or similar risks.

7. Retention limitation obligation

- To cease retention of personal data or remove the means by which the personal data can be associated with particular individuals when it is no longer necessary for any business or legal purpose.

- There is no specified retention period for personal data but this will be dependent on the purpose for which the personal data was collected. To retain the personal data based on organisation's policy due to legal or business purposes.

- No specified retention period for personal data but depends on the purpose for which the personal data was collected. To retain the personal data based on organisation's policy due to legal or business purposes.

8. Transfer limitation obligation

- It is a must to transfer personal data to another country only according to the requirements prescribed under the regulations, to ensure that the standard of protection provided to the personal data so transferred will be comparable to the protection under the PDPA, unless exempted by the PDPC.

9. Openness obligation

- To make information about data protection policies, practices and complaints process available on request.

- To designate one or more individuals as a Data Protection Officer to ensure that the organisation complies with the PDPA, including the implementation of personal data protection policies within the organisation. The business contact information of at least one of such individuals should also be made available to the public.

There are, however, exceptions to these rules and they are generally purpose-based. For example, some of these exceptions relate to emergency situations, investigations, publicly available data or where the personal data is used for evaluative purposes.

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 http://statutes.agc.gov.sg/aol/home.w3p*
- *Personal Data Protection Commission Singapore, available at https://www.pdpc.gov.sg/legislation-and-guidelines/overview*

CHAPTER 3

THE STUDY TEAM

3.1 Who Can Be A Principal Investigator (PI)?

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 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.

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. A fully registered medical practitioner, or a level 2 conditionally registered medical practitioner (please refer to subsequent section on “Special Considerations”);

b. A fully registered nurse;

c. A fully registered allied health practitioner; or

d. Research scientists, research fellows or health services research staff, or other personnel deemed eligible by the DSRB.

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 does not require a CTA / CTN / CTC from HSA, the individual should at least be:

a. A medical practitioner who is a 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. A senior staff nurse, with a member of the research team who must be an Associate Consultant and above;

c. An allied health staff who is a senior therapist / pharmacist, with a member of the research team who must be an Associate Consultant and above.

Clinical trials – PIs who are conducting clinical trials requiring a CTA / CTN / CTC from HSA must fulfil the minimum regulatory requirements to be a PI. Under the Health Products (Clinical

Trials) Regulations 2016 and Medicines (Clinical Trials) Regulations 2016, the PI must be either:

a. A locally registered doctor or dentist, who is a registered medical practitioner under the Medical Registration Act or a registered dentist under the Dental Registration Act.

b. Fully registered associate consultant and above, or a level 3 conditionally registered associate consultant and above (please refer to subsequent section on "Special Considerations").

For research conducted in NHG or partner institutions, the PI should be a staff of NHG or the partner institution. 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 within NHG or its partner institutions is in compliance with GCP and all other applicable guidelines and regulations.

3.1.2 Minimum Qualifications for Dentists to be PIs

Minimal risk studies – Fully registered, conditionally registered and temporarily registered dentists can be PIs of minimal risk (i.e. Expedited or Exempt) research studies.

Greater than minimal risk studies – Fully registered, conditionally registered and temporarily registered dentists who are Associate Consultants and above can be PIs of greater than minimal risk (i.e. Full Board) research studies.

Additionally, the following set of conditions must be fulfilled before a conditionally / temporarily registered dentist can be approved as the PI for a study:

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 SDC; and

   iii. Based on the conditionally / temporarily registered dentist's current progress and technical and ethical competency, the conditionally / temporarily registered dentist is deemed competent to assume the role of PI and affirms that 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 as PI has been provided to the 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.

3.1.3 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 Visiting Consultant must also ensure that he / she has been given approval by the institution to be the PI for the study.

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 SMC.

   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 that

the conditionally registered doctor has adequate medical expertise to make medical decisions for the safety and welfare of subjects.

b. The conditionally registered doctor declares that his involvement in research as PI has been provided to SMC and no objection has been received from SMC.

c. The DR and IR / IO approve of the conditionally registered doctor to be the PI of the study.

III. Multi-Centre Studies Between Two or More Clusters

If the research study involves two or more institutions from different clusters and the PI for the study is from an institution outside of the NHG cluster, it is necessary to have a PI from the NHG or partner institution.

IV. Multi-Centre Studies Involving SingHealth and NHG Institutions

From 1st October 2014, cross-cluster research applications (i.e. multi-centre studies between NHG/ NHG-partner institutions and SingHealth / SingHealth-partner institutions) 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 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.

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

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 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.

3.2 Minimum Training Requirements for Investigators and Study Team Members

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.

3.2.1 Training Courses

The minimum training requirements comprise 3 types of trainings:

a. Collaborative Institutional Training Initiative (CITI);

b. Good Clinical Practice (GCP) course;

c. Financial conflict of interest (FCOI) training.

Each of these trainings is described below in more detail.

I. Collaborative Institutional Training Initiative (CITI)

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

When setting up your CITI account, you must affiliate with “National Healthcare Group – Singapore” in order to access the correct curriculum. You should select the appropriate modules within CITI to read according to the type of research study(ies) you are intending to conduct.

CITI certification is currently mandatory for:

- PIs and site PIs conducting research studies other than clinical trials; and
- Co-investigators.

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

Module Type	Module Title	Module ID (on CITI platform)
Research ethics modules	Belmont Report and CITI Course Introduction	1127
	History and Ethics of Human Subject Research	498
	Informed Consent	3
	Social and Behavioural Research (SBR) for Biomedical Researchers	4
	Records-Based Research	5
	Populations in Research Requiring Additional Considerations and/or Protections	16680
	Conflicts of Interest in Research Involving Humans**	488
NHG-specific modules	NHG-Singapore. Overview of Domain Specific Review Board (DSRB) Review Process**	810
	NHG-Singapore. Overview of the Regulatory Framework and Guidelines in Singapore	809
	National Healthcare Group – Singapore	808

** *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 operationalisation and conduct of clinical trials.

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

GCP certification is mandatory for PIs and site PIs conducting clinical trials.

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.

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 Research Involving Human Subjects (ID: 488).

(Please refer to footnote under table 10 above.)

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 2 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.

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

* Only study team members involved in the design, conduct and reporting of research 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 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

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

^ 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 NHG FCOI training requirements will apply to him / her.

3.2.4 Waiver of Minimum Training Requirements

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

Any program that qualifies as a research ethics training equivalent of CITI should be at minimum, an 8-hour programme. The programme should be organised and conducted by a reputable organisation, e.g. NHG institutions, NUS, HSA, etc. and should address the following topics:

a. History and principles of research ethics

b. Regulatory framework and guidelines in Singapore

c. Informed consent

d. Privacy and confidentiality Issues

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

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 clinical trials, either as a PI or site PI, within NHG or its partner institutions under the oversight of DSRB over the last six years.

b. The applicant must have enrolled at least one subject for these clinical trials.

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 attendance 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.

3.2.5 References and Further Reading

For more information, please refer to:
www.research.nhg.com.sg → Conducting Research → Minimum Training Requirements.

3.3 Responsibilities of a PI

The PI is the person primarily responsible for the 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. The PI will not initiate the study until he / she has received notification of DSRB Approval and regulatory authority approval (if applicable).

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 / clinical trial team designated by the PI to perform study-related procedures and / or make important research-related decisions.

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

Research coordinators / clinical research coordinators / study nurses are members of the study team who handle most of the administrative responsibilities of a research study, act as a liaison between investigative site and sponsor, and review all data and records before the monitor's visit. Synonyms include trial coordinator, clinical research 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.

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 physician (or dentist, where appropriate) who is the PI or a co-investigator of the research study should be 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 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.

UPIRTSO Reporting - The PI must report all unanticipated problems that occur during the conduct of a research project to the DSRB, in accordance with the timelines set by DSRB.

Compliance with Protocol – The PI should not implement any deviation from or changes of the protocol without agreement by the sponsor and prior review and documented approval from the DSRB of an amendment, except where necessary to eliminate an immediate hazard (s) to subjects.

Continuing Review Reports – The PI should submit written summaries of the study status of the research study to DSRB before the expiry date of the approval, or more frequently if requested by DSRB.

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 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, 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 comply with the plan.

3.3.6 Informed Consent of Trial 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 more information on UPIRTSOs, please refer to chapter 4.7 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs).

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:
www.research.nhg.com.sg → *Resources* → *Proper Conduct of Research SOP & Templates.*

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

Duration of Record-Keeping

a. Essential documents for therapeutic products or medicinal products used in HSA-regulated clinical trials should be retained for:

   - 2 years after the last of such registrations have been granted; or
   - 2 years after informing HSA of termination of the clinical trial; or
   - 6 years after completion of clinical trial;

   Whichever is the longest.

b. Essential documents for therapeutic products or medicinal products used in other clinical research studies should be retained for at least 2 years after the supply, putting to other use, disposal or export.

c. Essential documents for unregistered medical devices used in HSA-regulated clinical trials should be retained for:

   - 2 years after the last of such registrations have been granted; or
   - 2 years after informing HSA of termination of the clinical trial; or
   - 6 years after completion of clinical trial;

   Whichever is the longest.

d. Essential documents for registered medical devices used in HSA-regulated clinical trials, or any medical device used in clinical research studies, should be retained for:

- The projected useful life of the medical device; or
- 2 years after the supply, putting to other use, disposal or export;

Whichever is longer.

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 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:
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

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 a 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).

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)
- Study administrator(s)

Any addition(s) or removal(s) of the abovementioned study team members to / from the study team member list must be informed 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. Approval must be received before the changes to the study team members may be implemented.

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)

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 – A significant financial interest means any ownership 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.

NHG 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 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 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 $50,000 in value. 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 that have a cumulative monetary value of $25,000 or more, 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 excluding the costs of conducting the clinical study (e.g. a grant to the investigator or to the institution to fund the investigator's on-going research or compensation in the form of equipment) and other reimbursements such as retainers for on-going consultation or honoraria.

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 must 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. Annual FCOI Declaration

The FCOI declaration cycle is an annual process, and is held from 01 December (of the current year) to 31 January (of the next year). The validity of the FCOI declaration form will be from the date the form is submitted during the cycle, until 31 December of the next year. Investigators 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 the declaration of their financial status. The completed form is to be submitted to the DSRB FCOI secretariat (DSRB_FCOI@nhg.com.sg).

If any study team member has 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 August 2017, this declaration would be valid only from August 2017 till December 2017.

II. 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).

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.

III. Other Notable Time points for Submitting FCOI Declarations

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

Submission Time Point	What To Do	Document(s) To Submit
At initial DSRB application	The PI will need to submit a separate Study Team Member List if there are team members NOT listed in Section B1(ii) of the DSRB application form (e.g. research nurses, research coordinator, etc.), and these study team members are involved in the design, conduct or reporting of research in institutions under the oversight of DSRB.	The Study Team Member List is to be attached in the initial DSRB application form.
At continuing review	The PI will need to submit a separate Study Team Member List if there are team members NOT listed in Section B1(ii) of the DSRB application form (e.g. research nurses, research coordinator, etc.), and these study team members are involved in the design, conduct or reporting of research in institutions under the oversight of DSRB.	The Study Team Member List 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(ii) of the DSRB application form), the PI will need to ensure that the new study team member:

- Completes the applicable FCOI training requirements (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. 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.

The PI will be informed by the DSRB on the management plan to eliminate or mitigate the identified conflicts of interest.

3.5.5 References and Further Reading

For more information, please refer to:
www.research.nhg.com.sg → Conducting Research → Minimum Training Requirements → Financial Conflict of Interest (FCOI) Training Requirements.

3.6 Institutional Conflict of Interest (ICOI)

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, PIs are required to submit their research protocols to the ICOI secretariat if they are sponsored by a biomedical research-related for-profit organisation or a philanthropic unit associated with a biomedical research-related for-profit organisation.

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

4.1.1 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 http://www.research.nhg.com.sg**.**

To help researchers navigate the ROAM system, ROAM guidebooks are available at: 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 15th 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 1st 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 received after the abovementioned deadlines will be tabled for the next month's Full Board meeting.

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: www.research.nhg.com.sg → Ethics & Quality → Apply for Ethics Approval → Ethics Review 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:

a. PI'S discipline – A research study will be triaged to the domain that reviews the discipline under which the study may be categorised.

b. 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 1st 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:
www.research.nhg.com.sg → Ethics & Quality → DSRB Announcements →
Updated FAQs on the Mutual Recognition of Research Ethics Review Between SingHealth-CIRB and NHG-DSRB.

4.2 Submission of New Applications

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 / waiver of documentation 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. Data collection forms;

f. Copy of the approved grant application (including DHHS-approved study protocol and sample consent form, if one exists);

g. Investigator's Brochure and other available safety information (for industry-sponsored clinical trials);

h. Recruitment materials intended to be seen or heard by potential subjects, including email solicitations and physician letters (if used);

i. Written information intended to be provided to subjects (if used);

j. Curriculum vitae (CV) of PIs and co-investigators, updated within the past one year;

k. Financial disclosure statement;

l. Relevant publications.

In addition, applicants may be requested to submit:

a. Clinical trial agreement (for industry-sponsored research);

b. Documentation relating to non-approval of study by another IRB;

c. Translated ICF(s) and translation certificate(s), or main English ICF accompanied by the translated short consent form(s);

d. Any other relevant documentation that the DSRB may specifically request;

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.

4.2.2 Materials for Subject Recruitment

Any materials to be used to publicise 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 study;

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. Name and address of the institution conducting the research;

c. 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. 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 subjects will not be charged for taking part in the investigation. Advertisements may state that subjects 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 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 subjects who participate in the research. The DSRB will consider the following issues while reviewing the payment arrangements:

a. Payment to the subjects for participation is not considered a benefit, but a reimbursement for the subjects’ time and expenses incurred.

b. The amount and proposed method and timing of payment should not present any undue influence.

c. Payment to subjects should be pro-rated, and not be contingent upon the subjects 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 subjects:

Table 14: Guidelines for research subject payments

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

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:
www.research.nhg.com.sg → Ethics & Quality → DSRB FAQ → Question 2.

Payment should be made via cheques payable to "**National Healthcare Group Pte Ltd**" and enclosed with an acknowledgement slip indicating the DSRB Reference Number. The cheque should be sent to the address below. Please ensure that the cheques are submitted early as the DSRB will not be able to release the approval letters if payment has not been received.

Cheques should be sent to:

NHG Domain Specific Review Board (DSRB)
3 Fusionopolis Link
#03-08 Nexus@one-north
Singapore 138543

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:

a. Exempt Review

b. Expedited Review

c. 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.

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 subjects can be identified, directly or indirectly through identifiers linked to the subjects;

b. Any disclosure of the human subjects' responses outside of the research could reasonably place subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

EXEMPTION CATEGORY 3 – Identifiable Subjects 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 subjects 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 collection or 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 subjects cannot be identified, directly or through identifiers linked to the subjects. 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.

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, 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, 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 subjects;

b. Identification of subjects 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 the 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.

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 subjects, 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 subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, 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 subjects, 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 subjects, 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 subjects to Full Board review.

Table 15: Maximum allowable total blood draw volumes

Body Weight (Kg)	Body Weight (lbs.)	Total Blood Volume (mL)	Maximum Allowable Volume (mL) for Children (= 3% of total blood volume) drawn in a 90-day period	Maximum Allowable Volume (mL) for Adults (= 5% of total blood volume) drawn in a 90-day period
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.

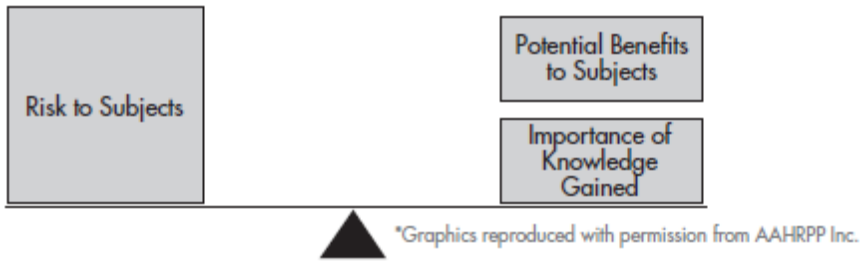
For further details on how to complete the ROAM application form, please refer to the ROAM guidebooks at:
www.research.nhg.com.sg → Resources → ROAM Guidebooks

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



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;

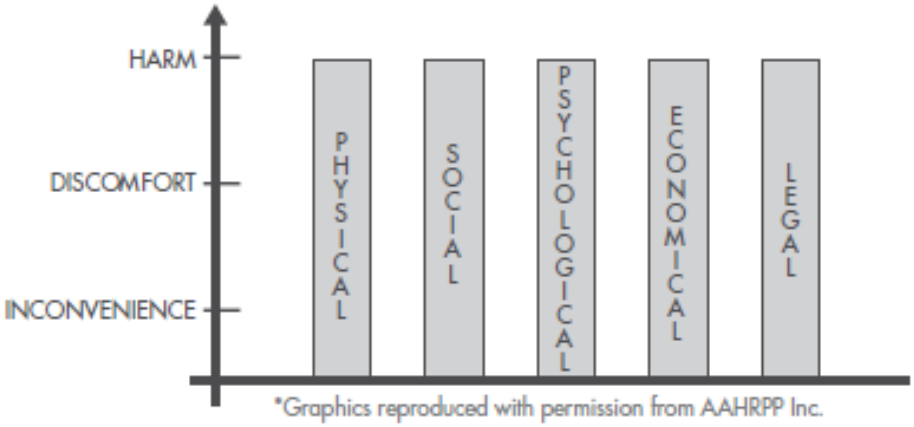
b. Psychological – e.g. psychological effects following survey asking sensitive questions;

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

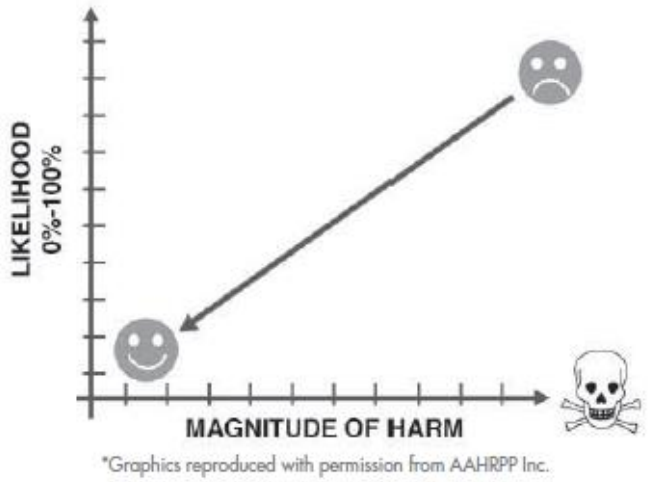


Only research-related risks should be considered, while risks associated with treatment that the subject would undergo even if not participating in the research and disease progression need not be considered while assessing research related risks.

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, 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).

Review Criteria

All research proposals that intend to enrol human subjects 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 subjects is equitable;

c. Informed consent will be sought, and appropriately documented;

d. Adequate provision for monitoring of data to ensure safety, protection of privacy of research subjects 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.

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

4.4 Outcome of Review

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. Subjects 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. 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.

d. 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.

e. 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.

f. 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.

g. 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.

h. The DSRB / REC will carefully and fairly evaluate the PI's appeal in reaching its final decision. The DSRB's / REC's decision will be 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.

i. The DSRB's / REC's decision is final. The PI cannot appeal further against this decision.

j. 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

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

Any deviation from, or a change of, the approved study 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 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. CATEGORY A (Major amendments) – The DSRB 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.

b. CATEGORY B (Minor amendments) – The DSRB will determine if the changes to the protocol affect the risk-benefit ratio of the study. Changes to the protocol that pose risks which are not more than minimal, or new procedures added that fit within the categories eligible for expedited review, will fall into this category.

c. CATEGORY C (Administrative amendments) – Administrative changes such as change in addresses, contacts, etc., and correction of typographical and grammatical errors fall into this category.

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 subjects involved in the study;

c. Addition of any study procedures that are of greater than minimal risk;

d. Increase in study subjects 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:
www.research.nhg.com.sg → Ethics & Quality → DSRB FAQ → Question 2.

Payment should be made via cheques payable to "**National Healthcare Group Pte Ltd**" and enclosed with an acknowledgement slip indicating the DSRB Reference Number. The cheque

should be sent to the address below. Please ensure that the cheques are submitted early as the DSRB will not be able to release the approval letters if payment has not been received.

Cheques should be sent to:

NHG Domain Specific Review Board (DSRB)
3 Fusionopolis Link
#03-08 Nexus@one-north
Singapore 138543

4.6 Continuing Review

Continuing review is required by the DSRB as long as the study is collecting or analysing 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 often 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.

If the study approval expires, no research activities, including 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 subjects;

b. All subjects have completed all research-related interventions; and

c. The research remains active only for long-term follow-up of subjects.

(For a multi-centre study, the Expedited review procedure may be used by DSRB when all of the above are satisfied for NHG 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 subjects have been enrolled – i.e. no subjects have ever been enrolled into the study at NHG 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 FOLLOW UP ONLY – The study is permanently closed to new subjects, all subjects 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 subjects and the remaining research activities are limited to data analysis.

e. COMPLETED – There will be no more research activities, including contact with subjects 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

When the study status of a research study remains unchanged as “Last Patient Last Visit Over, Data Analysis Ongoing” for more than two years, the DSRB will write to the PI to determine if active data collection has permanently ended and if analysis is conducted on data that has been permanently de-identified.

If these criteria are fulfilled, the PI will be advised to set the status as “Completed” and encouraged to register a Standing Database or Tissue Repository via the ROAM Standing Database or Tissue Repositories Application Form.

For more information, please refer to chapter 8 Standing Databases and chapter 9 Tissue Repositories.

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. Study amendments since the last review;

e. Assessment of the current risk, potential benefits, and the overall risk / benefit ratio of the study;

f. Research findings, if any;

g. Complaints about the research, if any;

h. Non-compliance reports, if any;

i. Any other relevant information, especially information about the risks associated with the research.

4.7 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

4.7.1 Definitions

ADVERSE EVENT – Any untoward or unfavourable medical occurrence in a patient or clinical investigation (during which) subject (was) administered 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.

4.7.2 Reportable Events

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

The criteria for reporting to DSRB include all problems that are:

a. Unexpected; and

b. Related or possibly related to study.

Table 16 below provides a summary of the types of events / problems 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 resulting in death	All other problems
Description of Event / Problem	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
Timeline for Initial Report	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
Timeline for Follow-Up Report	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.

I. Assessment of Reported Problems

The PI must make a judgment about the expectedness, of a reported problem. If the problem 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 problem is expected or unexpected. An unexpected problem 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, a problem more

specific or more severe than described in the Investigator's Brochure would be considered unexpected. An unexpected problem 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.

II. 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).

4.7.3 Reporting Timelines

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

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.

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

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

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

SERIOUS ADVERSE EVENT (SAE) – In relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research 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).

PIs must report all SAEs to the sponsor, except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. PIs must also report to the sponsor, 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 by the sponsor in 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, i.e. MOH and / or HSA.

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/content/moh_web/home/legislation/legislation_and_guidelines/human-biomedical-research-act.html.*

- *Clinical Trials Guidance – Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products Used in Clinical Trials, Health Sciences Authority, available at http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Clinical_Trials/Overview/Regulatory_Guidelines.html.*

4.8 Non-Compliances / Study Deviations

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. Information given by other staff within the institution;

c. Information given by other members of the research team;

d. Monitoring reports;

e. Audit reports;

f. 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, i.e. 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 neither serious nor continuing, the DSRB will require the PI to provide an explanation and outline the 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. Referring the study for an independent audit;

b. Modification of the study protocol;

c. Modification of the information disclosed during the consent process;

d. Providing additional information to past subjects;

e. Notifying current subjects of the additional information (required when such information may relate to subjects' willingness to continue to take part in the research);

f. Requiring current subjects to provide re-consent for continued participation;

g. Modification of the continuing review schedule;

h. Monitoring of the research study, including the consent documents;

i. Suspension of the research;

j. Termination of the research;

k. Obtaining more information pending a final decision;

l. Referral to other organisational entities (e.g. legal counsel, risk management, institutional official);

m. Mandating that the investigator attend additional training programmes;

n. Requiring the investigator to work with a senior researcher (mentor) for a period of time;

o. Disqualifying the investigator from conducting any research for a period of time;

p. Other actions appropriate to the context of the non-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, please refer to:

- *Clinical Trials Guidance – Notification of Serious Breach, Health Sciences Authority, available at http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Clinical_Trials/Overview/Regulatory_Guidelines.html.*

4.9 Changes in Study Status

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 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 subjects;

c. Serious or continuing non-compliance with the regulations or DSRB policies;

d. Emergence of new information suggesting increased risk to human subjects;

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;

e. Any other issue(s) deemed significant by the DSRB.

4.9.3 Study Completion

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

a. The research is permanently closed to the enrolment of new subjects;

b. All subjects 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 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 will request for additional information.

4.10 Other Notifications

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

The DSRB requires that informed consent 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 / her willingness to participate in a particular research study, after having been informed of all aspects of the research study that are relevant to his / 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 following considerations should be kept in mind while conducting an informed consent discussion. Exceptions to these requirements 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.

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 taken by the PI or any qualified member of the study staff who is listed in the DSRB application form as the designated person(s) for conducting the informed consent discussion. Any change to study staff / study role for obtaining consent should be submitted to the DSRB for review and approval. For clinical trials that are regulated by HSA, only an investigator who is a qualified practitioner is allowed to obtain informed consent from the subject. Individuals who are not qualified practitioners are not allowed to obtain consent, but may assist in the consent process for such studies. However, 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. Informed consent discussion should take place in person. Consent documents should not be mailed to subjects with instructions to call back with questions, or to sign and mail back.

f. Informed consent should be obtained before initiation of the study i.e. before any procedures performed solely for research are carried out.

g. The informed consent discussion must be conducted in a language understandable by the subject.

h. The informed consent process is not a one-time event carried out prior to enrolling research subjects, but should be an ongoing process throughout the duration of the study. Investigators must inform a subject of any important new information that may affect his/her 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. A memo distributed to subjects for their information;

    ii. An addendum to the previously signed ICF, to be signed again by the subject;

    iii. A revised ICF to be signed by the subject.

i. 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.

In general, consent for study participation must be taken from the subjects. In cases where the legal representative may be required to consent on behalf of the subjects, the DSRB will assess the requirement based on the subjects' population being studied or other special circumstances as detailed in chapter 5.7 When a Legal Representative is Required.

5.2 Developing the Informed Consent Form (ICF)

5.2.1 Required Elements of Informed Consent

The following elements must be present in the ICF:

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 subjects will be maintained and that notes the possibility that the regulatory authorities, IRB, and sponsor's monitors may inspect the records.

f. For research involving more than minimal risk, 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 participant, 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.

In the case of the removal, donation or use of human tissue for research, in addition to the required elements stated in above, the following required elements must also be present in the ICF:

a. 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.

b. 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. Any biological sample(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 sample(s) to be discarded or destroyed (e.g. upon withdrawal) if the biological sample(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 sample(s) for the research.

c. An explanation as to whether any compensation is provided and an explanation as to whether any medical treatments are available if injury occurs, for instance arising from the process of tissue donation and, if so, what they consist of, or where further information may be obtained.

d. Any additional costs to the subject that may result from participation in the research or as a consequence of donating tissue.

e. Whether individually-identifiable information obtained from the tissue donor will be used for future research.

f. Where applicable, whether biological material taken from the tissue donor will be destroyed, discarded or stored and used for future research.

g. A statement about whether, and the circumstances under which, the donor or the person authorised to give consent, will be contacted for further consent.

h. Whether the tissue donation would result in the use of the donor's tissue in an individually-identifiable form.

i. A statement about whether the tissue will be used in restricted human biomedical research involving human-animal combinations.

j. A statement about whether the donor or the person authorised to give consent would wish to be re-identified in the case of an incidental finding if the future research expressly provides for such re-identification.

k. Whether the tissue will be exported or removed from Singapore to a place outside Singapore.

5.2.2 Additional Elements of Informed Consent

Where appropriate, one or more of the following elements should also be detailed in the ICF:

a. 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.

b. Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent.

c. Any additional costs to the subject that may result from participation in the research.

d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

e. 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 subjects.

f. The approximate number of subjects involved in the study.

g. Possibility of randomisation to placebo, study or comparator arms.

h. Anticipated pro-rated payment, if any, for reimbursement of travel, meal or other expenses incurred due to participation in the research.

i. 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.

j. A statement that any biological sample(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 sample(s) to be discarded or destroyed (e.g. upon withdrawal) if the biological sample(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 sample(s) for the research.

k. When the research involves tests such as HIV testing that require mandatory reporting to the MOH if positive, this should be disclosed in the ICF, as amended / updated in the MOH mandatory reporting policy.

l. If the research involves genetic testing or DNA banking, the applicable issues in DNA banking and genetic research should be included.

m. If the research involves establishing a specimen / tissue repository, the applicable issues in specimen collection for tissue / specimen repositories should be included.

n. Any other information that is, in the DSRB's judgment would add meaningfully to the protection of the rights and welfare of subjects.

o. A statement of the intended research use of his personal data, including whether his tissue sample with personal data could be sent out of Singapore to an overseas collaborator.

5.2.3 General Considerations for the ICF

The following aspects should be considered when drafting ICFs:

a. SECOND PERSON – The ICF should be written in second person style. This allows the document to convey 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.

b. SIMPLICITY – The information presented in the ICF should be in a manner understandable to the subject. The ICF should avoid the use of technical and/or complex scientific terminologies, and should instead be worded in a format readable by laypersons.

c. EXCULPATORY LANGUAGE – The ICF should not contain any exculpatory language through which the subject is made to waive, or appears to waive legal rights or releases or appears to release the investigator, the sponsor, or the institution from liability for negligence.

d. 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.

e. 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 Template to develop the consent form. The PI may also contact the DSRB secretariat for advice on developing the ICF.

The NHG DSRB Informed Consent Form Template is available for download at: www.research.nhg.com.sg → Resources → Ethics Forms & Templates.

5.3 Study Team Members Authorised to Take Consent

Informed consent should be taken by the PI or any qualified member(s) of the study team who is / are listed in the ROAM application form as the designated person(s) 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 study staff / study team roles delegated to take consent should be submitted to the DSRB for review and approval.

5.3.1 Consent for Clinical Trials

QUALIFIED PRACTITIONER – Under the Health Products Act, 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.

For HSA-regulated clinical trials, only an investigator who is a qualified practitioner is allowed to obtain informed consent from the subject.

Individuals who are not qualified practitioners are not allowed to obtain consent, but may assist in the consent process for clinical trials. 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 process.

5.4 Documentation of Informed Consent

5.4.1 General Requirements for Consent Documentation

Each subject or his / her legal representative must sign and date a copy of the 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.

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, namely:

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 medical records.

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 / translator, verification of the appropriate legal representative for consent);

d. Whether a copy of the signed ICF was given to the subject.

Documentation in medical records is not required if the study does not involve access to medical records, such as a survey study, or observational epidemiological study. However, minimally-required information on the informed consent process should be documented in other source documents.

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 illiterate.

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 / her thumbprint on 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;

The person taking consent should document and clearly describe the informed consent process in the subject's medical records.

5.5 Subjects who are Unable to Read

When a subject or his / 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.

a. The written ICF and any other written information to be provided to the subject should be read and explained to the subject or his / her legal representative.

b. The participant or his / 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 understood by, the subject or his / her legal representative; and

   ii. Informed consent was freely given by the subject or his / her legal representative.

e. The study team member conducting the consent discussion should personally sign and date the ICF. A complete copy of the signed ICF should be given to the subject or his / her legal representative.

5.6 Non-English Speaking Subjects

5.6.1 Use of Translated ICFs

The preferred method of taking consent for non-English speaking subjects is always to provide the subjects with the ICF written in a 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 English 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 English ICF into the language understandable by the subject is preferred. Submission of the translated consent forms to DSRB should be accompanied by a letter of certification from the translator or translation service.

For investigator-initiated studies where the costs of translation are of concern, a certified translation is not required; documents translated by an individual fluent in the given language are acceptable. A letter from the translator describing his / her qualifications to perform the translation should be provided with the translated documents.

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: 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 by the subject, and as an alternative for investigator-initiated studies (for all types of research), oral presentation of informed consent information may be used and documented using:

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 written in the translated language, 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:

a. The short consent form should state that the elements of informed consent have been orally presented to the subject;

b. The short consent form should be printed in a language understandable by the subject;

c. 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. (The study team member obtaining consent cannot be the impartial witness.)

d. The subject / subject's legal representative, the study team member obtaining consent and the impartial witness must sign on both the DSRB-approved English language ICF and the short consent form;

e. The subject / subject's legal representative must be provided with a 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 document. A document footer (stating the document version number and date) and page number (i.e. Page X of Y) must be included as a common reference for the entire document.

The PI must submit all language versions of the short consent form appended together with the DSRB-approved English language ICF to DSRB, for approval prior to the use of these documents. Separate sets of documents should be submitted for each translated language.

The NHG DSRB Short Consent Form templates are available in three local languages (Mandarin, Malay and Tamil). These templates are available for download at: www.research.nhg.com.sg → Resources → Ethics Forms & Templates.

5.7 When a Legal Representative Is Required

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 subject is not capable of giving legally effective informed consent, such as in any of the following circumstances:

a. Where the subject is a minor;

b. Where the subject is cognitively impaired;

c. Where the subject 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

For research conducted in emergency situations, when prior consent of the subject is not possible, the consent of the participant's legal representative (if he / she is present) should be requested.

Where prior consent of the subject is not possible, and where the subject's legal representative is not contactable 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.

5.8.1 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, a specialist in the specialty relating to the research and who is not involved in the research study as a researcher or supervisor must give written certification that the following have been compiled with to the best of his / her knowledge:

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 participant'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 / legal representative / 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

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 DSRB and HSA must be provided with documentation from the PI and 2 independent specialists (who are not conducting the trial) certifying 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 / her medical condition;

c. It is not feasible to obtain consent from the subject's legal representative within the window period within which the investigational product must be administered; and

d. Neither the subject, nor his / 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 / her medical condition, and if at any time, the subject regains capacity to give consent, the PI must ensure that, at the earliest feasible opportunity:

a. The subject is given a full and reasonable explanation of the required elements of informed consent; and

b. Consent of the person is obtained, to continue being a subject in the trial.

If the consent of the subject in the clinical trial in an emergency situation cannot be obtained because of his / her medical condition, the PI must ensure that, at the earliest feasible opportunity (including during the window period):

a. All reasonable efforts are made to contact the subject's legal representative;

b. The legal representative is given a full and reasonable explanation of the required elements of informed consent; and

c. The legal representative's consent is obtained for the person to continue being a subject in the trial.

If the consent of the subject in the clinical trial in an emergency situation cannot be obtained because of his / 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;

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 / legal representative / any family member objects to the subject's continued participation in the trial, the subject should be immediately discontinued.

5.9 Consent on the Use of Human Tissue or Health Information for Research in Deceased Persons

When the prospective research subject or tissue donor is a deceased person, the appropriate consent:

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;

b. For the removal or use of human tissue for research from the deceased person;

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 Consent and Information Sheets

In some instances, PIs may wish to replace signed consent with verbal consent. The DSRB will consider approving such requests in limited circumstances

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.

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.

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. When there is a possible legal, social or economic risk to the participant entailed in signing the ICF, e.g. illegal immigrants, or HIV antibody-positive individuals who might be identified as such by signing the ICF.

c. When the study involves only a telephone interview.

The scenario given on the next page 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, R. Amdur and E. Bankert.
- NYU SoM Guidance Document - Guidelines of Requests for Waiver of Consent - Version 1 – 07/07.

5.11 Waiver of Informed Consent

The DSRB may approve a consent procedure that does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent provided the DSRB finds and documents that:

a. The research involves no more than minimal risk to the subjects;

b. The waiver or alteration will not adversely affect the rights and welfare of the subjects;

c. Whenever appropriate, the subjects will be provided with additional pertinent information after participation;

d. The research could not practicably be carried out without the waiver or alteration;

e. The research is not subject to FDA regulations;

f. The human biomedical research or health information research would reasonably be considered to contribute to the greater public good.

Updates on Waiver of Informed Consent Requirements under HBRA

The requirements for studies to qualify for a waiver of informed consent are slated to change, following the implementation of Part 2 (Fifth Schedule) of the HBRA and its subsidiary legislation.

Investigators should note that:

- Studies involving the collection of individually-identifiable health information obtained or compiled before the implementation date will be allowed to qualify for a waiver of informed consent, if the DSRB determines that the abovementioned criteria are fulfilled.

- Studies requesting for a waiver of informed consent, and involving the collection of individually-identifiable health information obtained or compiled after the implementation date, will be subject to the new requirements outlined in the subsidiary legislation to the HBRA.

The date of commencement and implementation of Part 2 (Fifth Schedule) of the HBRA and its subsidiary legislation will be announced by MOH in due course.

5.11.1 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 results would not affect any clinical decisions related to the individual's care.

c. Research could not be practicably carried out without the waiver: Identifying and contacting hundreds of potential subjects, while not impossible, would not be practicable for a medical record review where the results would not change the care that the individuals have already received. It is also not practical to obtain consent from subjects who are no longer on follow-up, lost to follow-up or deceased. However, if any subjects are still undergoing follow-up, it will be more difficult to justify why obtaining consent from these subjects will not be feasible.

d. 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.

CHAPTER 6

RESEARCH IN VULNERABLE POPULATIONS

6.1 Research Involving Children

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 should not be construed as assent.

CHILDREN – Persons who have not attained legal age for consent to treatments or procedures involved in the research, 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 – In relation to a child, 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.

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.

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/ permission 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/ permission 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;

iii. The intervention or procedure is likely to yield generalisable 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/ permission of their parents or guardians (or the legal representative as stipulated in the applicable regulations if different).

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 as listed under Condition for Research Involving Children, 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.

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 investigator shall 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 person below the age of 21 years who is or was married, with the consent of that person;

b. In the case of a person below the age of 21 years who is not and was never married, with the consent of that person 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 (the investigator should determine if the legal representative of the minor (if below 21 years of age) has sufficient understanding and intelligence to give informed consent); and

ii. There is a reasonable prospect that participation in the clinical trial will directly benefit that child, unless:

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 Therapeutic 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; and

E. The negative impact on the wellbeing of subjects involved in the trial is minimised and low.

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.

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.

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. The parent who has legal custody is the legal representative for the child.

b. When the child is illegitimate, the mother has sole legal responsibility for the care and custody of the child. The mother is the legal representative for the child.

c. The following individuals are legal representatives 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 and

    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 Parental Consent

WAIVER OF PARENTAL CONSENT / PERMISSION – Parental consent / permission 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 waive parental consent / permission, provided the following are adequately met:

a. The research is designed for conditions or for a subject population for which parental or guardian consent / permission 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.

In such cases, the PI should work with DSRB to devise alternative procedures for protecting the rights and interests of children approached for participation, such as the appointment of special guardians for the children.

For HIV / STD research that poses less than minimal risk to children, the DSRB may consider a waiver of parental consent / permission if the study meets both of the following criteria, in addition to the criteria set out above:

d. Potential subjects have attained the legal age for consent for sexual activity (i.e. 16 years old); and

e. 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 – Where the child lacks sufficient understanding and intelligence to give consent, they may possess the ability to assent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether or not they wish to participate in the research. This is especially so if the research does not involve interventions likely to be of benefit to the child, and the child can comprehend and appreciate what it means to be a volunteer for the benefit of others.

In general, the DSRB recommends that assent be obtained from children who are over six years old. The DSRB will determine whether all or some of the children are capable of assent by considering the following:

a. The nature of research;

b. The age, status, condition of the proposed subject; and / or

c. Maturity and psychological state of proposed subject.

Children who have been provided with the full explanation of all the required elements of the informed consent, but are unable to sufficiently understand and give consent 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.

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: www.research.nhg.com.sg → Resources → Ethics Forms & Templates.*

WAIVER OF ASSENT BY THE CHILD - The DSRB may determine that the assent of the child is not necessary (unless prohibited by the applicable regulations) when all of the following are met:

a. The children are not capable of providing 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 assent can be waived using the criteria for waiver of the consent process even when the children are capable of assenting, if the criteria set out in chapter 5.11 Waiver of Informed Consent are met.

6.1.6 Special Circumstances – Wards of Court

Additional protections need to be in place when a research involves children who are wards of court or any other institution or entity. Where the research involves greater than minimal risk to the subject with no prospect of direct benefit to the individual subject, (i.e. category 3) the research must either be related to their status as wards, or else be 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

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 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 assent and their parents' permission 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.

6.2.2 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 provide data 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.

NEONATES OF UNCERTAIN VIABILITY – Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart 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.

NONVIABLE 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.

6.2.3 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 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

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 – Technically, 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., 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 (i), (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.

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, consultation with healthcare providers involved in the care of these patients should be performed 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:
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; and

ii. If the legal representative is below 21 years of age, he / she 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 the adult, unless:

(1) The objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;

(2) The trial is conducted in subjects having a disease or condition for which the therapeutic product being tested in the trial is intended;

(3) There is some direct benefit for the group of subjects involved in the trial;

(4) The foreseeable risks to the subjects involved in the trial are low; and

(5) The negative impact on the wellbeing of subjects involved in the trial is minimised and low.

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.

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.

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.

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

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

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. An example of a moderate risk study would be a phase IV trial studying the 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.

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:

- 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 serious adverse events to DSRB. For a minimal risk research study involving multiple sites, this function could be managed by the PI at each site or the lead PI for the entire research study.

- INDEPENDENT EXPERT(S) – For a moderate risk research study or an investigator-initiated clinical trial involving single or multiple sites, it is recommended that data safety monitoring be performed by an expert or group of experts in the disease who are familiar with the agent being investigated. Using an independent expert or team of experts is particularly helpful in monitoring the 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) – This is a committee that is established specifically to monitor data throughout the course 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 large sponsor-initiated, blinded studies involving multiple sites, it is recommended that a formal DSMB be appointed.

II. Safety Monitoring Plan

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 day-to-day 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 it is evident that one treatment group is doing better than the others. The research study may be stopped for efficacy as the research question has been answered with a sufficient level of certainty.

- Futility – This occurs when it is evident that the treatment group is not substantially different from, or may even be faring worse than, the other groups (e.g. comparator or placebo groups). This may also occur when too many subjects have withdrawn from the study, such that it is difficult to obtain conclusive data even though the study is continued. When it is evident that the research question will not be answered by completing the study, the study may be stopped for futility.

- 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. For investigator-initiated clinical trials that are regulated by HSA, monitoring should be performed in accordance with the ICH GCP standards. The monitor should be independent of the research team, appropriately trained and have the scientific and / or clinical knowledge needed to monitor the trial adequately. The PI may seek the assistance from their institution's CRU / research office on finding a suitable monitor for their study.

b. Sponsor-initiated clinical trials should outline a plan consistent with the ICH GCP guidelines for monitoring.

II. 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 plan should describe how the outcome of data and safety monitoring are communicated to other participating study sites, as well as to the DSRB.

III. Transfer of Personal Data

No personal data (identifiable information) should be transferred to a country outside Singapore except in accordance with the requirements prescribed under the PDPA. In addition, if the data were to be transferred to another country, a copy of the study application document or data should be kept in Singapore at the study site.

7.2 Privacy and Confidentiality

PRIVACY is the act of maintaining respect for the patients. To protect a patient's privacy, only healthcare professionals who have access to the patient for their clinical care should make contact with the patient, for the purpose of inviting him / her to participate in a research.

CONFIDENTIALITY refers to respecting the patient's data. To avoid breaches in confidentiality, the PIs should store identifiable data in a secure location with access limited only to members of the research team.

7.2.1 Restricting Access to Research Data and Medical Records

The study proposal should include details on how the security of research data will be maintained. Examples include the use of password protection on research study databases, scheduled changes to passwords, and / or restricting access to research study databases on an "as-needed" basis.

The PI must ensure that only authorised persons are allowed to access medical records for research. The patient must also have given prior written consent for such access, unless the DSRB has granted a waiver of consent.

To access clinical records for research purposes, the PI must seek permission from the custodian of the standing database.

When electronic databases are used, the PI should ensure that:

a. Electronic databases should be stored in a secure computer, preferably within local drives on the computer, rather than in common or shared drives.

b. The databases should be password protected.

c. The databases should not contain subject identifiers (as defined in the above section), and the data linking subject identifiers and the subject identification codes should be stored separately.

d. When data is stored in portable media such as CD ROMs, USB drives, external hard drives etc., subject identifiers should never be stored in the same destination medium.

e. Research data sent to individuals outside the institution should not contain any subject identifiers, unless specific approval has been obtained from DSRB.

7.2.2 Determining if Data is Identifiable

Data is considered identifiable if one or more of the following information elements are present:

a. Subject's name

b. Address – street name

c. Address – postal code

d. Elements of dates (except year) related to a subject. For example, date of birth, admission or discharge dates, date of death

e. Telephone number

f. Fax number

g. Electronic mail address

h. NRIC number

i. Medical record numbers

j. Health plan beneficiary numbers

k. Account numbers

l. Certificate / license numbers

m. Vehicle identification number and serial numbers including license plate

n. Medical device identifiers and serial numbers

o. Web URLs

p. Internet protocol (IP) address

q. Biometric identifiers (finger and voice prints)

r. Full face photographic images

s. Any unique identifying number, characteristic or code link to identifier (code).

7.2.3 Removing Subject Identifiers

DCFs and CRFs should not contain information directly identifiable to a subject, such as name, identity card number, address, etc. Each subject should be assigned a unique subject identification code to be used on the DCFs, CRFs, SAE 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 (e.g. subject initials and date of birth) 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. Using the example of subject initials and date of birth, the following alternatives may be proposed for the DCF / CRF:

a. Collecting either the subject's initials or the date of birth, but not both;

b. Substituting the subjects initials with code while retaining the date of birth; or

c. Collecting only the year of birth instead of the full date of birth, together with the subject initials.

7.3 Compensation for Research-Related Injuries

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 NMEC Ethical Guidelines on Research Involving Human Subjects states that “in the event of any significant injury, the subject must be entitled to receive compensation regardless of whether there may or may not have been legal negligence of legal liability on any other basis” (i.e. no fault basis).

c. 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: www.research.nhg.com.sg → Resources → Ethics Forms & Templates.

7.4 Audits and Inspections

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 study drug 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 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.

The Investigator File Contents Template and Pre-Audit Checklist are available for download at: www.research.nhg.com.sg → Resources → Proper Conduct of Research SOPs & Templates.

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.

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?

j. What are the study procedures and how are they performed?

k. What is the procedure for investigational product accountability?

l. What is the procedure for randomisation and unblinding?

m. How are the biological samples handled?

n. Is refrigeration required for biological samples? If yes, is a temperature 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 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?

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).

The NHG Research QM Study Review Checklist is available for download at:
www.research.nhg.com.sg → Resources → Proper Conduct of Research SOPs & Templates.

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:
www.research.nhg.com.sg → Resources → Proper Conduct of Research SOPs & 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 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.

From March 2017, only a selected group of PIs will be notified through email to participate in the self-assessment programme using the PI Self-Assessment Form. The form is administered via an online question-based checklist which takes approximately 15 minutes to complete.

The NHG Research Quality Management unit will review the PI Self-Assessment Form and make recommendations on any aspect(s) of the study conduct that may require improvement. Once the PI receives these written recommendations, he / she will be required to respond to NHG Research Quality Management within the indicated timeline, on the actions taken to rectify the named issues. In the event of queries, the PI may contact the Research Quality Management team at researchquality@nhg.com.sg.

The Principal Investigator Self-Assessment Form is available for download at:
www.research.nhg.com.sg → Resources → Proper Conduct of Research SOPs & Templates.

CHAPTER 8

STANDING DATABASES

This chapter is currently under review while awaiting further regulatory and policy updates.

For the latest announcements and information on standing databases, please refer to the NHG Research Website.

We seek your kind understanding for any inconvenience caused.

8.1 Standing Databases

This chapter is currently under review while awaiting further regulatory and policy updates.

For the latest announcements and information on standing databases, please refer to the NHG Research Website.

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CHAPTER 9

TISSUE REPOSITORIES

This chapter is currently under review while awaiting further regulatory and policy updates.

For the latest announcements and information on tissue repositories, please refer to the NHG Research Website.

We seek your kind understanding for any inconvenience caused.

9.1 Tissue Repositories

This chapter is currently under review while awaiting further regulatory and policy updates.

For the latest announcements and information on, please refer to the NHG Research Website.

We seek your kind understanding for any inconvenience caused.