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

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

a. Doctors - Fully registered medical practitioner, or a level 2 conditionally registered medical practitioner (please refer to subsequent section on “Special Considerations”)

b. Dentists - Fully registered/ conditionally registered/ temporarily registered dentists

c. Nurses - Registered nurse

d. Allied Health Staff – Registered allied health practitioner

e. Case managers, research scientists, research fellows and health services research staff, or as determined to be eligible by the DSRB

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

(a) The research involves locally registered products;

(b) The PI must have a PhD and/or PharmD and/or other appropriate Postgraduate Qualification, hold a primary appointment in a local institution and salaried by the institution, with a demonstrated track record of research for example, as evidenced by the award of nationally competitive funding, substantial publication record or a laboratory or clinical research program that carries out research in Singapore; and

(c) For interventional clinical trials, a locally-registered physician(s) should be involved as co-investigator(s) to provide direct medical supervision and monitoring of the trial subjects.

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

a. Doctors – Fully registered Associate Consultant and above, or who is a level 3 conditionally registered Associate Consultant and above (please refer to subsequent section on "Special Considerations");

b. Dentists – Fully registered/ conditionally registered/ temporarily registered Associate Consultant and above.

c. Nurses – Senior Staff Nurse (SSN) – Must have an Associate Consultant and above on the research team.

d. Allied health staff - Senior therapist / pharmacist, with a member of the research team who must be an Associate Consultant and above.

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

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

3.1.2 Special Considerations

I. Visiting Consultants

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

II. Conditionally Registered Medical Practitioners

- A level 2 conditionally registered medical practitioner is one who has fulfilled 0.5 years of practice at level 1 and has received at least an "above average" performance grading for the past 6 months.

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

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

a. The supervisor of the level 2 or level 3 practitioner must declare in writing that:
   i. He / She is aware of, and supports, the involvement of the conditionally registered doctor as PI;

   ii. He / She will provide guidance and include research activities in regular progress reports to the Singapore Medical Council (SMC); and

   iii. Based on the doctor's current progress and technical and ethical competency, the conditionally registered doctor is deemed competent to assume the role of PI, and affirms that the conditionally registered doctor has adequate medical expertise to provide medical care and decisions for the safety and welfare of subjects.

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

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

III. Conditionally/ Temporarily Registered Dentists

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

a) The supervisor of the dentist must declare in writing that:

   i. He/ she is aware of, and supports, the involvement of the conditionally/ temporarily registered dentist as PI;

   ii. He/ she will provide guidance and include research activities in regular progress reports to Singapore Dental Council (SDC); and

   iii. Based on the conditionally/ temporarily registered dentist's current progress and technical and ethical competency, the conditionally/ temporarily registered dentist has adequate dental expertise to provide clinical care and make clinical decisions for the safety and welfare of the subjects.

b) The conditionally/ temporarily registered dentist declares that his/ her involvement in research and PI has been provided to SDC and no objection has been received from SDC.

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

IV. Multi-Cluster Studies

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

- If the study is a grant-awarded study, the overall PI would be the person who is awarded the grant, and the application should be submitted to his / her cluster's IRB.

- If the study is an industry- or commercially-sponsored study, an overall PI would have to be selected and the application submitted to his / her cluster's IRB.

- If the study is an investigator-initiated (with no grant or funding required), the overall PI would be the person who initiated the study. The application should be submitted to his / her cluster's IRB.

- If the research project involves different clusters, and the overall PI for the research project is not from NHG or partner institutions; it would be necessary to have a Site PI from NHG or partner institution.

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

V. Multi-Centre Studies Within NHG and Partner Institutions

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

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

3.2 Minimum Training Requirements for Investigators and Study Team Members

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

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

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

3.2.1 Training Courses

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

I. Collaborative Institutional Training Initiative (CITI);

II. Good Clinical Practice (GCP) course;

III. Financial conflict of interest (FCOI) training;

IV. Research Institution (RI) Specific Training Minimum Requirements (e.g. HBRA training)

Each of these trainings is described below in more detail.

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

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

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

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

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

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

Table 10: CITI core modules

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

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

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

b. 5 elective modules, selected from the available list of elective modules. Modules may be selected based on investigators' area(s) of specialty, relevance to the study(ies) being conducted and/or individual interest.

2. Investigators conducting population health research (i.e. making submissions to DSRB domain F) are required to complete the following modules:

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

b. 5 elective modules, selected from the available list of Social, Behavioural and Educational (SBE)-related elective modules. These modules may be identified by the "SBE" suffix in their names. Modules may be selected based on investigators' area(s) of specialty, relevance to the study(ies) being conducted and / or individual interest.

II. Good Clinical Practice (GCP) Course

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

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

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

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

III. Financial Conflict of Interest (FCOI) Training Requirements

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

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

1. NHG-Singapore. Overview of Domain Specific Review Board (DSRB) Review Process (ID: 810)*;

2. Conflicts of Interest in Human Subjects Research (ID: 17464 or 488)*

(Please refer to footnote under table 10 above.)

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

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

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

- Where CITI is a minimum training requirement (i.e. for PIs conducting clinical research studies, or co-investigators), investigators will have to complete the CITI course as stipulated above. Completion of CITI will automatically ensure that the FCOI training requirements are met, as the FCOI-related training modules are encompassed within the CITI course requirements.

- Where CITI is not a minimum training requirement (i.e. for PIs conducting clinical trials, or other study team members), investigators and study team members will only be required to complete the 2 FCOI-related training modules listed above. It is not mandatory to complete the full set of 10 core modules and 5 elective modules in CITI.

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

IV. RI Specific Minimum Training Requirements

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

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

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

The NHG HBR ERC Course is also applicable to all:

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

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

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

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

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

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

3.2.2 Minimum Training Requirements for Staff from NHG and Partner Institutions

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

Table 11: DSRB minimum training requirements

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

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

3.2.3 Minimum Training Requirements for Staff from SingHealth and Partner Institutions

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

Table 12: CIRB minimum training requirements

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

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

3.2.4 Minimum Training Requirements for Staff from Other External Institutions

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

3.2.5 Waiver of Minimum Training Requirements

Waiver to complete the CITI or GCP courses

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

I. Criteria to Qualify for a Waiver of CITI Certification

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

a. History and ethics principles of research ethics

b. Regulatory framework and guidelines in Singapore

c. Informed consent

d. Privacy and confidentiality Issues

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

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

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

II. Criteria to Qualify for a Waiver of GCP Certification

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

a. The applicant must have conducted a minimum of five (5) clinical trials, either as a PI or site PI, within NHG or its partner institutions under the oversight of DSRB over the last six (6) years;

b. The applicant must have enrolled at least one subject for these clinical trials (stated in a); and

c. The applicant certifies that there were no major research ethics violations, non-compliances, unjustified DSRB SOP deviations, research misconduct and / or complaints for these clinical trials (completed and ongoing).

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

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

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

3.3 Responsibilities of a PI

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

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

The PI must adhere to the following declarations:

a. Ensure written approval/ notification/ acknowledgement is obtained from the IRB and relevant authorities (e.g. Ministry of Health (MOH), Health Sciences Authority (HSA), where applicable) prior to the start of the study or when instituting any changes to the protocol.

b. The PI will not initiate any change in protocol without prior written approval from the DSRB except when it is necessary to reduce or eliminate immediate risk to the subjects. Thereafter, the PI will submit the proposed amendment to the DSRB and other relevant authority(ies) for approval.

c. The PI will promptly report any unexpected or serious adverse events, unanticipated problems or incidents that occur in the course of the study, in accordance with applicable safety reporting guidelines.

d. The PI will maintain all essential documents and recognise that the DSRB and / or other regulatory authorities may inspect these records.

e. The PI understands that failure to comply with all applicable regulations, institutional and DSRB policies and requirements may result in the suspension or termination of this study.

f. The PI declares that there are no conflicting interests for any of the research personnel participating in the study, as well as their immediate family members. Should there be any conflicts of interest, the PI must declare these in the ROAM online application form and describe the plan to remove or manage the conflict of interest.

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

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

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

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

3.3.1 Qualifications and Agreements

The PI must be qualified by education, training and experience to assume the responsibilities associated with proper conduct of a research study, and should meet all qualifications specified by the applicable regulatory requirements.
For the conduct of clinical trials, a qualified practitioner under the Health Products (Clinical Trials) and Medicines (Clinical Trials) Regulations refers to an individual who is:

a. A registered medical practitioner under the Medical Registration Act (Cap. 174); or

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

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

3.3.2 Adequate Resources

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

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

3.3.3 Medical Care of Subjects

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

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

3.3.4 Communication with DSRB

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

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

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

3.3.5 Compliance with the Protocol

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

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

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

3.3.6 Informed Consent of Research Subjects

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

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

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

3.3.7 Safety Reporting

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

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

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

3.3.8 Other Obligatory Reporting Requirements

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

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

3.3.9 Records and Reports

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

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

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

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

Duration of Record-Keeping

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

a. the date where there is no more pending or contemplated application for registration under the Health Products Act of the therapeutic product/for a product licence for the medicinal product being tested in the clinical trial;

b. the expiry of 2 years after the last of such registrations is granted/after the last approval of such application for the medicinal product to be tested in Singapore;

c. where the clinical trial is terminated, the expiry of 2 years after HSA has been informed of the termination of the trial under regulation 12 of the Health Products or Medicines (Clinical Trials) Regulations 2016;

d. the expiry of 6 years after the conclusion of the clinical trial;

e. the expiry of such other period as HSA may direct in any particular case.

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

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

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

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

3.3.10 Clinical Research Materials (CRM)

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

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

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

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

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

3.3.11 Randomisation Procedures and Unblinding

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

3.3.12 Premature Termination or Suspension of a Trial

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

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

3.3.13 Conflict of Interest

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

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

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

3.3.14 Sponsored Clinical Trials

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

3.4 Change of PI and / or Study Team Members

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).

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

3.4.2 Changes in Study Team Members

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

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

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

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

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

3.5 Financial Conflict of Interest (FCOI)

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

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

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

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

3.5.1 Identifying FCOI

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

a. Financial interests (e.g. stocks, stock options or other ownership interests) in the assets or liabilities of any company that may benefit from the research activity.

b. Payments (e.g. salary, consultation fees, speaking fees, or honoraria) from any company that may benefit from the research activity.

c. Employment or executive relationships with any company that may benefit from the research activity.

d. Intellectual property rights or proprietary interests (e.g. patents, copyrights and royalties from such rights) related to the research.

e. Options or other compensation arrangements that could be affected by the outcome of the research.

3.5.2 Disclosure of Financial Interests to DSRB

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

a. Any compensation by any commercial sponsor company of the study in which the value of compensation could be affected by study outcome.

b. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.

c. Any equity interest in any commercial sponsor of the study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the investigator or study team member is carrying out the study and for one year following completion of the study.

d. Any equity interest in any commercial sponsor of the covered study if the commercial sponsor is a publicly held company and the interest exceed $10,000 in value or 10% of the voting stock or controlling interest of the commercial company (whichever is lower). The requirement applies to interests held during the time the investigator or study team member is carrying out the study and for one year following completion of the study.

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

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

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

3.5.3 Timelines for FCOI Declarations to DSRB

I. At initial Application to DSRB

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

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

II. Annual FCOI Declaration

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

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

III. FCOI Arising During Conduct of the Study

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

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

IV. Other Notable Time points for Submitting FCOI Declarations

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

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

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

- Completes the applicable FCOI training requirements, where applicable (please refer to chapter 3.2 for details);

- Submits a completed FCOI declaration form to the DSRB FCOI Secretariat; and

- Is added into the Study Team Member List submitted to DSRB during the annual continuing review.

3.5.4 Review and Management of FCOI

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

a. Disclosure of the conflict in the consent document;

b. Modification of research plan;

c. Divestiture of financial interest;

d. Severance of the relationship that created the conflict;

e. Training on conflicts of interest for all personnel involved in the research;

f. Disqualification from participation in all or a portion of the research; and/or

g. Audit of research by independent reviewers or review committees.

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

a) Increased monitoring or audit frequency by the Research Institution(s)/independent reviewer(s)/review committee(s);

b) Preventing the investigator(s) from receiving any Intellectual Property-related payouts during the interim period before there is sufficient evidence-based recommended usage of the investigational product/device;

c) Restricting the investigator(s)'s involvement in the research (e.g. he/she should not participate in the safety and efficacy assessments, data analysis, and/or report writing); and/or

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

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

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

3.6 Institutional Conflict of Interest (ICOI)

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

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

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

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

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