ADDENDUM TO THE INVESTIGATOR'S MANUAL

FOR DSRB BIOMEDICAL DOMAINS

2ND EDITION

VERSION 1.5
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Purpose

The Investigator's Manual (2nd Edition) was published in May 2013. Since then, there have been a series of research policy changes that the NHG Office of Human Research Protection Programme (OHRPP) would like to communicate to all NHG investigators and researchers. This addendum is a compilation of all policy and standard operating procedure (SOP) updates that have been amended since May 2013.

All chapter titles and page numbers printed in this addendum are referenced to the Investigator's Manual (2nd Edition). Text printed in *italics* describe the location and nature of the amendments that have been made from the original text. Text printed in **bold (with or without underline)** represents the revisions and/or additions that have been made from the original text.

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Chapter 1.1 – Office of Human Research Protection Programme (OHRPP)

Page 7 – This section has been revised as follows.

In its entirety, the OHRPP comprises **4** divisions:

a. **<u>DSRB Operations & Management</u> – 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 subjects in NHG and her institutions.**

b. **<u>Research Quality Management (RQM)</u> – 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. RQM also works with DSRB to ensure and continue high quality and efficient review of research applications.**

c. **<u>Research Education (RE)</u> – RE develops training programmes and educational support initiatives for investigators, as well as overseeing the propagation of Responsible Conduct of Research culture and education within the research community.**

d. **<u>Partnership & Outreach (P&O)</u> – 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.**

For more information, please visit our website at http://www.research.nhg.com.sg**.**

Chapter 1.4 – The Definition of Research

Page 18 – The definition of indirect human biomedical research has been expanded to include research involving human cadaveric tissues.

INDIRECT HUMAN BIOMEDICAL RESEARCH comprises any research that does not qualify as Direct Human Biomedical Research, and

a. that involves

   i. human subjects, or

   ii. human tissue **(including cadaveric tissue)**, or

   iii. medical, personal or genetic information relating to both identifiable and anonymous individuals, and

b. that is undertaken with a view to generating data about

   i. medical, genetic or biological processes, diseases or conditions in human subjects, or

   ii. of human physiology, or

   iii. the safety, efficacy, effect or function of any device, drug, diagnostic, surgical or therapeutic procedure (whether invasive, observational or otherwise).

Chapter 2.1 – Ethical Research

Page 23 – This section has been revised as follows.

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.

All organisational officials, researchers and research staff (including students involved in conducting research), DSRB chairpersons and members and employees of NHG's Human Research Protection Programme (HRPP), are required to abide by the following regulations and ethical standards:

a. Medicines Act;

b. Singapore Guideline for Good Clinical Practice (SGGCP), adapted from the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) E6 guidelines;

c. National Medical Ethics Committee (NMEC) ethical guidelines on research involving humans; and

d. Bioethics Advisory Committee (BAC) Guidelines for IRBs.

Chapter 4.4 – Unanticipated Problems Involving Risks To Subjects of Others

Page 68 – This section has been revised as follows.

Reporting to the DSRB

The time frame for the Principal Investigator to submit the reportable events to the DSRB is described below.

a. **For more than minimal risk studies (Full Board review), all problems involving local deaths should be reported immediately – within 24 hours after first knowledge by the investigator, regardless of causality and expectedness of the death event.**
b. **For no more than minimal risk studies (Exempt or Expedited review), problems involving local deaths that are related or possibly related to the study should be reported immediately – within 24 hours after first knowledge by the investigator.**
c. **All other problems must be reported as soon as possible but not later than 7 calendar days after first knowledge by the investigator.**

A local participant is one who is recruited from an NHG institution or an institution under the oversight of DSRB.

The DSRB secretariat will notify and send a report of the problem to the institutional officials and any other relevant agencies should the problem be (1) unexpected, (2) related or possibly related and (3) suggests research places subject or others at greater risk of harm. This report will contain the details of the problem along with the decision made by the Board

SPECIAL CONSIDERATIONS – In certain circumstances, for example, studies whereby the study design requires long term treatment-free follow up till death, the requirement to report all local deaths, regardless of causality and expectedness of the death event, within 24 hours of first knowledge by PI, does not provide additional information that would add meaningfully to the protection of the rights, safety and/or wellbeing of the subjects. The DSRB may alter the reporting requirements of local deaths, provided that the rights, safety and/or wellbeing of the research participants continue to be protected, **and provided that the REC and GCEO (where applicable) have approved the specific procedure.**
However, the DSRB Chairperson shall have the discretion to alter the reporting requirements of local deaths for individual studies if he/she has determined that it is a unique circumstance and therefore not necessary to obtain the approval of REC and GCEO.

Oncology Studies

The REC and GCEO have approved the alteration of the local death reporting requirements for 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. **Unrelated to the investigational product,**
c. **No clinically meaningful information that allows assessment of the risk-benefit relationship of the study,**
d. **No significant implications on the rights and welfare of the subjects.**

The reporting requirements are as follows:

	Local Death Occurring within 60 days (or less) after last dose	Local Death Occurring more than 60 days after last dose
Related (unexpected or expected)	**Preliminary report by PI within 24 hours of first knowledge**	**Preliminary report by PI within 24 hours of first knowledge**
Unrelated (expected or unexpected)	**Preliminary report by PI within 3 days of first knowledge**	**Routine reporting for Annual Continuing Review**

The PI is required to follow up with the detailed report after the preliminary report.

Note: Wherever possible, all unrelated and expected local death reports should be reviewed by a data and safety monitoring entity.

Chapter 4.5 – Non-Compliances / Study Deviations

Page 70 – The definition of "Study Deviation" and timeline for reporting of non-compliances and study deviations have been added to this section.

<u>STUDY DEVIATION</u> is an unplanned excursion from the study that is not implemented or intended as a systematic change.

- **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 Principal 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 participants.**

- **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 parts of the subjects to complete scheduled visits as required by the protocol.**

Page 71 – Amendments have been made to the sub-section on "Reporting to the DSRB" as follows:

The DSRB encourages reporting of non-compliances and study deviations by the Principal Investigator, members of the research team or other sources. When a report of non-compliance / study deviation is made by someone other than the Principal Investigator, 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 DSRB may receive an allegation or a report of non-compliance ***/*** **study deviation** by many means that include, but are not limited to:

a. Voluntary notification by the Principal Investigator.

b. The Principal Investigator's non-response to DSRB's queries / reminders for renewal.

c. Information given by other staff of the institution.

d. Information given by other members of the research team.

e. Monitoring reports.

f. Audit reports.

g. Complaints from research subjects.

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

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 non-compliances / deviations are substantial or will likely result in greater harm or greater likelihood of harm to the subjects.

If the non-compliance **/ study deviation** is valid and is neither serious nor continuing, the DSRB will require the Principal Investigator to provide an explanation and outline a corrective action to avoid repeating the non-compliance **/ study deviation**. If the Principal Investigator's reply is not satisfactory or is not forthcoming, this is 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 will provide an opportunity to the Principal Investigator to respond in person at a convened meeting, informal conference or in writing.

Chapter 5.1 – Important Considerations for the Informed Consent Process

Page 75 – Some revisions have been made to the following text on the informed consent process.

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.

c. Subjects should be approached in a conducive environment. For example, it would not be appropriate to approach a subject immediately before a procedure or surgery, while in labour, while under sedation and any other situation where a subject might feel compromised.

d. Informed consent discussion should be conducted by the Principal Investigator, or a qualified member of the study team who is listed in the DSRB Application Form as the designated person for conducting the informed consent discussion. **Any change to study staff, should be submitted to DSRB for review and approval. For clinical trials and other clinical research that requires a Clinical Trial Certificate (CTC), only a locally registered medical doctor or dentist is allowed to obtain informed consent from the subjects. Non-doctors/non-dentists may be delegated to participate or assist in the consent process for studies with CTC, however the Principal Investigator must ensure that the delegated person is well-trained to conduct the consent process appropriately without compromising on the quality of the consent.**

e. Informed consent discussion should take place in person. Consent forms should not be mailed to subjects with instructions to call back with questions, sign and mail back.

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

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

h. Informed consent is not a one-time single event prior to enrolling research subjects, but must be a continuous ongoing process. Investigators must inform subjects of any important new information that may affect their willingness to continue participation. The DSRB must approve the method of notification prior to implementation. The method may include, but is not limited to any of the following:

    i. Information Letter.

    ii. Addendum to previously signed consent form, to be signed by subject.

    iii. Revised consent form to be signed by subject.

In general, consent to participation must be taken from the subject. In cases where the legally acceptable representative may be required to consent on behalf of the subject, the DSRB will assess the requirement based on the subject population being studied or other special circumstances as detailed in chapter 5.7 When a Legally Acceptable Representative is Required.

Chapter 5.2 – Elements of an Informed Consent Form

Page 77 – point g has been amended as follows.

Required Elements of Informed Consent

The following elements must be present in the consent document:

a. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

b. A description of any reasonably foreseeable risks or discomforts to the subject.

c. A description of any benefits to the subject or to others that may reasonably be expected from the research.

d. A disclosure of appropriate alternative procedures or courses of treatment, if any, **which might be advantageous to the subject**.

e. A statement describing the extent to which, if any, confidentiality of records identifying the subject will be maintained and that notes the possibility that the regulatory authorities, DSRB, the sponsor's monitors and/or any other authorised parties 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 subject, and whom to contact in the event of complaints or feedback about research.

h. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

i. The title of the research study, the Principal Investigator's name and contact details.

Page 78 – The additional elements of informed consent have been revised.

Additional Elements of Informed Consent

When appropriate, one or more of the following elements **of information should also be provided to each subject:**

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 subject.

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 it has not been anonymised.

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

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.

Page 80 – The following item is to be added after the sub-section on "FDA-Regulated Test Articles".

<u>Document footer and page number</u>: The version number and version date of the consent form should be clearly stated as a 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.

Chapter 5.4 – Documentation of Informed Consent

Page 82 – The following text in this section has been revised.

Each subject or his / her legally accepted representative must sign and date a copy of the DSRB-approved informed consent form prior to enrolment or any participation in any aspect of the study, unless the requirement is waived by the DSRB. The subject or his/her legally accepted representative must be given a copy of the signed informed consent form.

The DSRB may approve procedures for documentation of informed consent that involve any of the three options listed below. The DSRB will determine which procedure is appropriate for the research study being reviewed:

a. **A written informed consent form (in English or fully translated into another language) signed by the subject or legally acceptable representative; or**

b. **An English written informed consent form appended with a translated short consent form, with oral presentation; or**

c. **In limited circumstances, waiver of a signed written consent form.**

In most circumstances, the DSRB will require that informed consent be documented by the use of a written consent form approved by the DSRB and signed by the subject or the subject's legally accepted representative.

The study team member who conducted the informed consent discussion must personally sign and date the consent form. Additionally, the study team member is required to document in the subject's medical records the date of informed consent, and that a copy of the signed consent document was given to the subject.

In general a copy of the informed consent document should be placed in the medical records, to document the subject's participation in a research study. If the informed consent document is not placed in the medical records due to confidentiality reasons, the investigator should place a statement in the medical records indicating the subject's participation in the research study. 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. If a medical record will be created because of participation in a research study, the research subject should also be informed of this.

For any research study of more than minimal risk and all interventional research, the subject should be requested to inform his / her attending doctor of participation in the research study.

A non-therapeutic clinical trial (i.e. a trial in which there is no anticipated direct clinical benefit to the participant) should be conducted in participants who personally give consent, and who can sign and date the written consent form.

Chapter 5.6 – Non-English Speaking Subjects

Page 86 – The following section on "Use of the Short Consent Form" has been rewritten.

Use of the Short Consent Form

In the event where the informed consent form has not been translated and is not available in the 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. A DSRB-approved English language informed consent form serving as the written summary of the information to be orally translated and presented to the subject; and

b. A short consent form stating that the elements of informed consent have been presented orally to the subject or the subject's legally accepted 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 informed consent form 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 informed consent together with the short consent form.

The complete set of informed consent documents for non-English speaking subjects is constituted by the following:

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

The Short Consent Form Templates are available on the NHG Research website, under the Resources section:
http://www.research.nhg.com.sg/wps/wcm/connect/romp/nhgromp/resources/dsrb+forms+and+templates

Chapter 6.1 – Research Involving Children

Page 106 – Requirements on HIV / STD studies involving children have been added.

WAIVER OF PARENTAL PERMISSION – Parental permission may not be appropriate in cases such as in research involving child abuse or neglect.

The DSRB may waive parental permission, provided the following are adequately met:

a. The research is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants.

b. An appropriate mechanism for protecting the children who will participate as participants in the research is substituted.

c. The research is not US FDA-regulated.

In such cases, the Principal Investigator 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 permission if the study meets both of the following criteria, in addition to the criteria set out above:

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

b. The study is pertinent to children in this particular age group (i.e. 16 to 20 years old).

Chapter 7.1 – Recruitment Strategies

Page 124 – Under the sub-section "Payment to Research Subjects", the following typographical error in the table has been amended.

Investigators may refer to the following guidelines for payment to research subjects:

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

The payment amount takes into consideration the current local standard of living (year 2012) and may be revised when necessary.

Chapter 7.3 – Data and Safety Monitoring

Page 131 – The section on "Data Monitoring" has been renamed as "Data Accuracy and Compliance", and some of its text has been revised.

Data Accuracy and Compliance

The Principal Investigator 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 conducted under a Clinical Trial Certificate, monitoring should be in accordance with SGGCP. 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 of CRU / institution research office with the logistics of finding a suitable monitor.**

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

Page 132 – The section on "Frequency and Extent of Data Monitoring" has been renamed as "Frequency and Extent of Monitoring", and some of the wording has been revised.

Frequency and Extent of Monitoring

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 participants have been enrolled, or upon recognition of harm. The plan should state how often monitoring will be performed, **who will perform monitoring** and what data will be reviewed for **safety monitoring.**

Page 132 – The following two sections have been added after the section on "Frequency and Extent of Data Monitoring".

Communication of Outcome of Data and Safety Monitoring (For Multicentre Trials)

The plan should describe how outcome of data and safety monitoring are communicated to other participating sites and DSRB.

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 Personal Data Protection Act. 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.

Chapter 7.5 – Conflicts of Interest

Page 137 – This chapter has been substantially amended as follows:

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 participants or the credibility of the human subject protection program.

DHHS regulated studies: For DHHS-regulated studies, the DHHS reporting requirements will apply.

FDA regulated studies: For FDA-regulated studies, the FDA reporting requirements will apply.

Identifying Financial Conflicts of Interest

Financial interest related to the research means financial interest in the sponsor, product or service being tested. Some examples of financial interest related to the research of the investigators, study team members or their immediate family members (which include parents, siblings, spouse and each dependent child) include:

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.

Disclosure of Financial Interests to DSRB

All study team members involved in the design, conduct or reporting of research will be required to declare any financial interests related to the research study under the oversight of NHG DSRB.

Declarations made to the DSRB must state 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 exceeds $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 (SPOOS) are payments 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 ongoing research or compensation in the form of equipment) and other reimbursements such as retainers for ongoing consultation or honoraria.

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

Timeline for Declarations to DSRB

With effect from 01 Jul 2015, the Principal Investigator and all study team members involved in the design, conduct and reporting of research are each required to declare if they or their immediate family members have any existing financial interests in the research annually and within 30 days if there are any changes to the financial interest status.

The annual FCOI declaration cycle will be from 1 Jan to 31 Jan of each year and the validity will be from the date of FCOI declaration form submitted till 31 Dec of the same year. This declaration may be submitted to the DSRB FCOI Secretariat (DSRB_FCOI@nhg.com.sg).

If the Principal Investigator or a study team member misses the annual FCOI declaration cycle, they may still submit the declaration form. However, the declaration will only be valid until the next declaration cycle. For example, if the Principal Investigator or study team member submits the declaration form in August 2017, this declaration would be valid only from August 2017 till December 2017.

At every initial application and continuing review, the Principal Investigator will need to submit a separate Study Team Member List (if it was not submitted at the initial application) for team members NOT listed in Section B1(ii) (e.g. research nurses, research coordinator, etc.) of the ROAM application form and are involved in the design, conduct or reporting of research in institutions under the oversight of NHG DSRB. This list is to be attached in Section C of the initial Application Form or the Study Status Report for submission to the DSRB.

Financial conflicts of interests may also arise during the conduct of the study. If such interests arise, the investigator and/or affected study team members should declare these to the DSRB FCOI Secretariat as soon as possible, but not later than 30 calendar days following first knowledge of these conflicting interests.

Review and Management of Financial Conflicts of Interest

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

Special Considerations

If the DSRB detects that investigators and study team members have not declared any financial conflicts of interest, the issue will be addressed according to NHG Cluster HR policies NHG-HR-S1, General Conduct and NHG-HR-T1 to T6, Disciplinary Policy and Procedures. Investigators and study team members must also comply with Cluster HR Policy NHG-HR-S11 to S13, Gifts, Sponsorship and Entertainment when dealing with industry sponsors of research projects.

The DSRB may require the investigators and study team members to be re-educated on the disclosures and responsibilities related to financial conflicts of interest, when the investigators and study team members are found to be non-compliant with NHG's financial conflict of interest policies.

Management of Institutional Conflicts of Interest (ICOI)

Institutional Conflict of Interest (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 subjects research.

To manage institutional conflicts of interest, 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 NHG Research Ethics Committee or designated ICOI Review Committee / designee.

With effect from 01 January 2015, Principal Investigators 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 NHG DSRB has the final authority to ensure if the conflict of interest management plan is adequate and whether the research can be approved. The NHG DSRB will engage the ICOI Review Committee to consider all possible management plans before deciding to terminate any research.

Chapter 8.1 – Who can be a Principal Investigator?

Page 153 – The requirements to be the Principal Investigator of a greater than minimal risk study have been updated.

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 Principal Investigator for a greater than minimal risk study **that does not require a Clinical Trial Certificate**, 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 "*Requirements for Conditionally Registered Medical Practitioners*").

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.

For research conducted in NHG or partner institutions, the Principal Investigator 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 Principal Investigator has the responsibility for ensuring that the conduct of the research within NHG or its partner institutions is in compliance with SGGCP and all other applicable guidelines and regulations.

In addition to all the above requirements, Principal Investigators who are conducting clinical trials that require a Clinical Trial Certificate from HSA must fulfil the minimum regulatory requirements to be a Principal Investigator. Under the Medicines Act and Medicines (Clinical Trials) Regulations, the Principal Investigator must be either:

a. A locally registered doctor or dentist who is a

b. Fully registered associate consultant and above, or a level 3 conditionally registered associate consultant and above.

Chapter 8.2 – Minimum Training Requirements

Page 157 – The minimum training requirements for research have been revised for Principal Investigators, co-investigators and all other study team members involved in the design, conduct and reporting of research. These revised requirements are as described below.

The intent of having minimum training requirements is for Principal Investigators, **co-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.

Courses

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI) – This is a web-based training programme **on human research subject protection.**

From 1st January 2015, Principal Investigators and co-investigators are required to complete 10 core modules and 5 elective modules inclusive of the CITI Financial Conflict of Interest (FCOI) course (a sub-component of the CITI Programme).
All other study team members (involved in the design, conduct or reporting of research will be required to declare any financial interests related to the research study under the oversight of NHG DSRB) are required to complete the 2 CITI FCOI modules.

The 10 core modules that Principal investigators and co-investigators will be required to complete are:

1. **Introduction (ID: 757)**
2. **History and Ethical Principles (ID: 498)**
3. **Informed Consent (ID: 3)**
4. **Social and Behavioral Research for Biomedical Researchers (ID: 4)**
5. **Records-Based Research (ID: 5)**
6. **Research With Protected Populations - Vulnerable Subjects: An Overview (ID: 7)**
7. **NHG - Singapore. Overview of Domain Specific Review Board (DSRB) Review Process (ID: 810)** ***(CITI FCOI module)***

8. **NHG-Singapore. Overview of the Regulatory Framework and Guidelines in Singapore (ID: 809)**

9. **National Healthcare Group – Singapore (ID: 808)**

10. **Conflicts of Interest in Research Involving Human Subjects (ID: 488) (New Compulsory Requirement) *(CITI FCOI module)***

The 2 CITI FCOI modules that all other study team members will be required to complete are:

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)**

Investigators and study team members who have not obtained their CITI certification as of 1st January 2015 (i.e. completed 9 core modules and 5 elective modules) will be required to complete the following additional 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)**

Investigators and study team members who have obtained their CITI certification before 1st January 2015 will need to complete the above 2 modules from the CITI FCOI course.

This is to ensure that all researchers are adequately informed of NHG's revised financial conflict of interest policy, which has come into effect from 1st January 2015.

The CITI Program is available online at http://www.citiprogram.org.

SINGAPORE GUIDELINE FOR GOOD CLINICAL PRACTICE (SGGCP) COURSE – In general for the conduct of research studies, Principal Investigators and co-investigators who have completed the SGGCP course do not need to complete the CITI program. The SGGCP course may be used as an alternate minimum requirement.

Principal Investigators who are conducting clinical trials will have to complete the SGGCP course as the minimum training requirement, regardless of whether the CITI certification has previously been obtained.

Investigators who have completed the SGGCP course as their alternate or minimum training requirement will also be required to complete the following additional modules on CITI related to NHG's financial conflict of interest policy:

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)**

Page 157 – Some requirements in the sub-section "Waiver of Minimum Training Requirements" have been revised.

Waiver of Minimum Training Requirements

If the Principal Investigator or co-investigator has attended any other course relevant to research ethics, the Principal Investigator or co-investigator may apply for a waiver of the requirement to complete the CITI or SGGCP course program. This will be reviewed for approval by the DSRB and the waiver may be granted on a case-by-case basis.

CRITERIA TO QUALIFY FOR WAIVER – Any program that qualifies as a research ethics training equivalent of CITI should be at minimum, an 8-hour program. The program should be organised and conducted by a reputed body – for example NUS, NHG institutions and HSA 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

Experienced investigators who have assumed the roles and responsibilities of a Principal Investigator 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 trial studies, either as a Principal Investigator or site Principal Investigator, 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 SGGCP course attendance will be reviewed and approved by the REC Chairperson or any other members appointed by the REC Chairperson to do so.

From 1st January 2015, Principal Investigators and co-investigators who have obtained the SGGCP certificate, received approval for a waiver of CITI or SGGCP certification will still be required to complete the following 2 additional modules on CITI:

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)**

This is to ensure that all researchers are adequately informed of NHG's revised financial conflict of interest policy, which will come into effect from 1st January 2015.

Chapter 8.3 – Responsibilities of the Principal Investigator

Page 160 – The definition of "Study Administrators" in the original text has been replaced with the following:

RESEARCH COORDINATOR / CLINICAL RESEARCH COORDINATOR / STUDY NURSE 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: trial coordinator, clinical research coordinator, research coordinator, clinical coordinator, clinical trial coordinator.

Page 161 – The following changes have been made to the sub-sections listed below.

Medical Care of Subjects

Any qualified physician (or dentist, when appropriate) who is the Principal Investigator or a co-investigator of the research study should be responsible for all research related medical (or dental) decisions.

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

(Last paragraph has been removed.)

Communication with DSRB

The Principal Investigator 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 Principal Investigator 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 Principal Investigator 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 Principal Investigator should submit written summaries of the study status of the research study to the DSRB before the expiry date of the approval, or more frequently, if requested by the DSRB.

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

Page 165 – The sub-section on "Conflict of Interest" has been revised to require all study team members to declare any conflicts of interest to the DSRB.

The Principal Investigator **and each member of the research team** must declare on the application form to the DSRB whether they or their immediate family members have any financial interests related to the research study. 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.

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

Please refer to chapter 7.5 Conflicts of Interest for more details on identifying and managing conflicts of interest.

9.4 PRINCIPAL INVESTIGATOR SELF-ASSESSMENT PROGRAMME

The Principal Investigator (PI) Self-Assessment Programme is a quality assurance component under the NHG Research Quality framework at OHRPP. This programme aims to familiarise investigators with requirements of proper research conduct and identification of areas in their conduct of research that may require improvements.

The PI Self-Assessment Form (PISAF) is a tool used to facilitate self-monitoring, and is available on ROAM. It is an effective way for investigators to assess if the research study has been conducted in compliance with applicable guidelines.

Effective from January 2016, the programme will be revised so that only selected studies with a higher risk of non-compliance will need to perform mandatory self-assessment.

For PIs with more than 1 PI initiated studies, the NHG RQM will select no more than 1 study for self-assessment.

The NHG RQM **unit** will review the **PISAF** and make recommendations on any aspects of the study conduct that may require improvement. Once an investigator receives these written recommendations, he / she will be required to respond to NHG RQM within the indicated timeline on the actions taken to rectify the issues.