CHAPTER 4

SUBMISSIONS TO DSRB

4.1 The Application Process

4.1.1 Research Online Administration and Management (ROAM) System

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

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

4.1.2 Timeline for Submission of Applications

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

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

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

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

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

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

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

4.1.3 Endorsement by the Institution

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

- Once the PI submits an application, it will be automatically routed to the DR for endorsement.

- After the DR has endorsed the application, it will be automatically routed to the IR for endorsement.

- DSRB will receive the application only after both the DR and IR have endorsed it.

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

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

4.1.4 Triaging of Studies to the Relevant DSRB Domain

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

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

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

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

b. Disease studied in the research study – Depending on the primary disease group that is being studied in the research study, the study will be triaged to the domain that includes experts in this disease group.

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

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

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

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

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

4.1.6 Collaborative Agreement Between Other IRBs and NHG DSRB

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

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

4.2 Submission of New Applications

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

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

4.2.1 Supporting Documents Required for New Applications

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

a. A completed ROAM online DSRB application form;

b. ICF / application for waiver of informed consent;

c. Study protocol (this is mandatory for clinical trials involving drugs, medical devices and surgical procedures);

d. Questionnaires, surveys, videotapes and other such research tools (if used);

e. Copy of the approved grant application or notification of award (if the study is a US federally funded research, the approved grant application, study protocol and sample consent form, etc.);

f. Investigator's Brochure and other available safety information (for all HSA regulated clinical trials);

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

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

i. Incidental Findings Management Plan;

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

In addition, applicants may be requested to submit:

a. Data Collection Form;

b. Financial disclosure statement;

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

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

e. Any other relevant documentation to be given to subjects when, in the judgment of the DSRB, the additional information would add meaningfully to the protection of the rights, safety and / or wellbeing of the subjects,

f. Any other relevant documentation that the DSRB may specifically request.

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

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

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

4.2.2 Materials for Subject Recruitment

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

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

- Finders' fees are defined as payments from the investigator or sponsor to a person who refers a potential subject.

- Recruitment bonuses are defined as payments from the sponsor to an investigator or organisation based on the rate or timing of recruitment.

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

a. Newspaper advertisements;

b. Posters, bulletins, flyers, brochures;

c. Email messages;

d. Invitation letters to potential subjects.

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

a. Letters to doctors for referring potential subjects;

b. Stories in newspapers or magazines that mention the research project;

c. Listing of clinical trials on internet websites, when the format is limited to basic trial information such as protocol title, purpose of study, protocol summary, basic eligibility criteria, study site location and how to contact the site for further information.

I. Preparing Advertisements for Subject Recruitment

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

a. Where the material will be used e.g. newspaper, radio including number of times the advertisement will be run;

b. Locations of posters / flyers,

c. Final copy of the advertisement for printed material, and / or video or audio tape that will be used for the broadcast.

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

a. That volunteers are being recruited for research;

b. The name and address of the institution conducting the research;

c. The condition under study and / or the purpose of the research;

d. In summary form, the criteria that will be used to determine eligibility for the study;

e. A brief list of participation benefits, if any (e.g. no-cost health examination);

f. The time or other commitment required of the subjects;

g. The location of the research and the person or office to contact for further information.

The advertisement should not, either explicitly or implicitly:

a. State or imply a certainty of favourable outcome or other benefits beyond what is outlined in the ICF and protocol;

b. Make claims that the drug, device or biologic is safe or effective for the purposes under investigation;

c. Make claims that the test article is known to be equivalent or superior to any other drug, biologic or device;

d. Use terms such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational;

e. Promise “free medical treatment,” when the intent is only to say participants will not be charged for taking part in the investigation. Advertisements may state that participants will be paid, but should not emphasise the payment by such means as larger or bold type. Advertisements should not state the amount that will be paid;

f. Include any exculpatory language;

g. Make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with currently approved labelling.

II. Payment to Research Subjects

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

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

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

c. Payment to participants should be pro-rated, and not be contingent upon the participants completing the study.

d. Payment of a small proportion as an incentive for completion is acceptable, providing the incentive is not coercive.

e. Compensation for participation should not include coupons for discount on the price of the study material after the product is approved for marketing.

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

Table 14: Guidelines for research subject payments

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

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

4.2.3 Applicable Fees for New Submissions

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

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

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

4.3 Review of Submitted Applications

4.3.1 Categories of Review

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

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

- DSRB application form 2 – Exempt category
  This category is for the submission of all Exempt review studies.

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

I. Exempt Review

II. Expedited Review

III. Full Board Review

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

I. Exempt Review

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

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

EXEMPTION CATEGORY 1 – Normal Educational Practices and Settings
Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:

a. Research on regular and special education instructional strategies; or

b. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

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

i. All of the research is conducted in a commonly accepted educational setting (e.g., a private or public school).

ii. The research involves normal educational practices (e.g. comparison of instructional techniques).

iii. The study procedures do not entail a significant deviation in time or effort from those educational practices already existent at the study site.

iv. The study procedures do not involve an increase in the level of risk or discomfort beyond normal, routine educational practices, including physical education.

v. The study procedures do not involve deception or withholding of information.

vi. The study procedures do not involve sensitive topics, such as sexual behavior of individual participants or population. A sensitive survey is one that deals with socially questionable or highly personal issues or alcohol and/or drug abuse.

vii. Provisions are made to ensure the existence of a non-coercive environment for all students, including those who choose not to participate.

viii. The school or other agency grants written approval for the research to be conducted.

ix. Educational tests of (i) knowledge, (ii) mastery, or (iii) skills.

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

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

a. Information obtained is recorded in such a manner that human participants can be identified, directly or indirectly through identifiers linked to the participants;

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

EXEMPTION CATEGORY 3 – Identifiable Participants in Special Circumstances

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

a. The human participants are elected or appointed public officials or candidates for public office; or

b. Statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

EXEMPTION CATEGORY 4 – Collection of Existing Data

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

EXEMPTION CATEGORY 5 – Public Benefit or Service Programmes

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

a. Public benefit or service programmes;

b. Procedures for obtaining benefits or services under those programmes;

c. Possible changes in or alternatives to those programmes or procedures;

d. Possible changes in methods or levels of payment for benefits or services under those programmes.

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

i. The research or demonstration project is conducted pursuant to specific federal statutory authority.

ii. There is no statutory requirement for IRB review of the project.

iii. The project does not involve significant physical invasions or intrusions upon the privacy of participants.

iv. The exemption is authorized by the federal funding agency.

v. The program under study delivers public benefit or service (e.g., financial or medical benefits) or service (e.g., social, supportive, or nutritional services).

EXEMPTION CATEGORY 6 – Taste and Food Evaluation and Acceptance Studies

Taste and food quality evaluation and consumer acceptance studies:

a. If wholesome foods without additives are consumed; or

b. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe.

Special Circumstances

The criteria for exemption do not apply for:

a. Research involving prisoners;

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

c. FDA-regulated research.

Exempt Review Determination

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

II. Expedited Review

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

The Expedited review process may be used for:

a. Initial review of new research proposals;

b. Continuing review;

c. Review of study amendments;

d. Review of modifications requested by DSRB to secure approval (conditional approval).

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

a. The research proposal presents no more than minimal risk to research participants;

b. Identification of participants and / or their responses does not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatising, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal;

c. The research is not classified;

d. The research activity is in the one of the categories of research listed below.

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

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

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

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

a. From healthy, non-pregnant adults who weigh at least 50 kg. For these participants, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week.

b. From other adults and children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

c. For collection of blood samples that do not fulfil the two criteria above, the research study will undergo a Full Board review.

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

a. Hair and nail clippings in a non-disfiguring manner;

b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

c. Permanent teeth if routine patient care indicates a need for extraction;

d. Excreta and external secretions (including sweat);

e. Uncannulated saliva collected either in an un-stimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue;

f. Placenta removed at delivery;

g. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labour;

h. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings,

j. Sputum collected after saline mist nebulisation.

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

a. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subjects or an invasion of the subject's privacy;

b. Weighing or testing sensory acuity;

c. Magnetic resonance imaging without contrast;

d. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography,

e. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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

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

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

III. Full Board Review

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

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

a. From other adults, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected, not more than 5% of Total Blood Volume may be drawn over 24 hours, with a maximum amount of 500ml on a single withdrawal of blood.

b. From other children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected, not more than 3% of Total Blood Volume may be drawn over 24 hours, with a maximum amount of 200ml on a single withdrawal of blood.

c. If the maximum amount of blood is withdrawn from a subject, no subsequent blood should be drawn for 3 months.

d. From healthy, non-pregnant adults who weigh at least 50 kg, the allowable maximum amount of blood drawn will be assessed and determined by the Full Board committee.

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

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

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

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

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

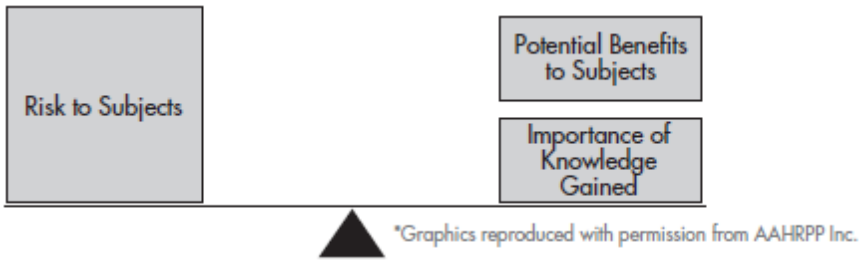
For further details on how to complete the ROAM application form, please refer to the ROAM guidebooks at https://www.research.nhg.com.sg > Resources > ROAM Guides.

4.3.2 Review Considerations and Criteria

Risk-Benefit Assessment

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

Figure 2: Benefit-risk ratio



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

a. Physical – e.g. bruising after blood draw, study drug related adverse events;

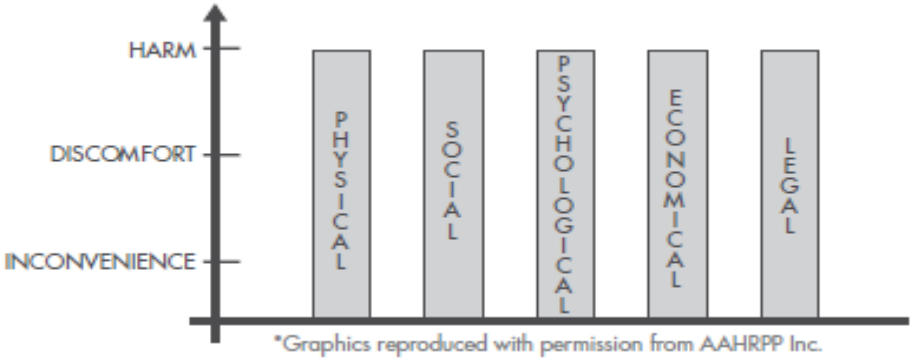
b. Psychological – e.g. psychological effects following survey asking sensitive questions;

c. Social – e.g. breaches in confidentiality revealing that a subject suffers from a psychiatric illness;

d. Economic – e.g. additional expenses to be borne by subject due to participation in research;

e. Legal – e.g. mandatory reporting of drug abuse discovered during the research may cause legal problems for the subject.

Figure 3: Research-related risks

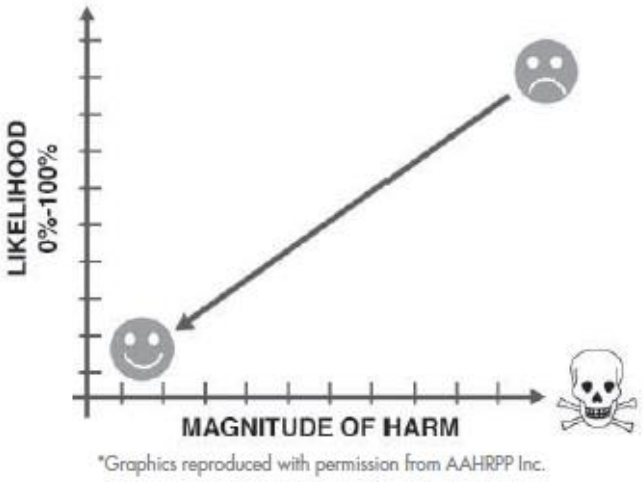


Only research-related risks should be considered, while risks associated with treatment that the subject would undergo even if not participating in the research and disease progression need not be considered while assessing research related risks.

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

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

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



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

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

a. Physical – Procedures already being performed on the research subjects for diagnostic or treatment purposes should be used, instead of performing additional tests for research. For example, drawing extra blood during a routine blood draw for treatment rather than drawing blood specifically for research;

b. Psychological – Debriefing after the completion of the research;

c. Social – Ensuring confidentiality is maintained especially while dealing with sensitive information;

d. Economic – Ensuring that the subject does not have to pay out of pocket for research-related expenses and that institution covers treatment for research-related injuries;

e. Legal – Informing the subject during consent process if mandatory reporting is required or employing a study design that assures anonymity;

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

a. Management of the event – The PI should ensure that adequate medical care is provided to the subject for treatment of adverse events.

b. Assessment of the event – The PI should assess the risk, expectedness, and relation of the event to the study.

c. Reporting of the event – The PI must report the event to the DSRB, and where applicable, to other relevant authorities.

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

Review Criteria

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

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

a. Risks are minimised, and are reasonable in relation to anticipated benefits;

b. Selection of participants are equitable;

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

d. Adequate provision for monitoring of data to ensure safety, protection or privacy or research participants and confidentiality of data collected;

e. Additional protection for vulnerable populations.

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

a. Risks to subjects are minimised by using procedures which are:
    i. Consistent with sound research design;

    ii. Do not unnecessarily expose subjects to risk; and

    iii. When appropriate, already being performed for diagnostic or treatment purposes.

b. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result**:**

    i. The DSRB will consider only those risks and benefits that may result from the research (as distinguished from the risks and benefits of therapies subjects would receive even if not participating in the research).

    ii. The DSRB will not consider possible long-range effects of applying knowledge gained in the research as among those research risks (such as possible effects of the research on public policy) that fall within the purview of its responsibility.

c. Selection of subjects is equitable – In making this assessment, the DSRB will take into account the following:

i. The purposes of the research;

ii. The setting in which the research will be conducted;

iii. Special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

d. Informed consent will be sought from each prospective subject or the subject's legal representative, in accordance with, and to the extent described in chapter 5.0 Informed Consent and chapter 6.1 Research Involving Children.

e. Informed consent will be appropriately documented, in accordance with, and to the extent described in chapter 5.0 Informed Consent.

f. When appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.

g. When appropriate, there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

h. When some or all of the subjects are likely to be vulnerable to coercion or undue influence – such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons – additional safeguards have been included in the study to protect the rights and welfare of these subjects.

i. The HBRA prohibits the commercial trading of human tissue (whether for research, therapy or any other purpose). Therefore, the DSRB will not approve any research that involves the use of human tissues that are purchased commercially.

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

4.4 Outcome of Review

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

a. Approved

b. Conditionally approved

c. Tabled for next convened meeting

d. Not approved

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

a. APPROVED – The research proposal is approved as submitted. The PI is not required to change any aspect of the proposal or consent document.

b. CONDITIONALLY APPROVED – There are no major problems with the study. If the PI addresses the issues listed by the DSRB, the study can be formally approved. Participants must not be recruited into the study until the final approval has been issued.

c. TABLED FOR NEXT CONVENED MEETING – A proposal may be tabled if there are significant questions raised that need further information from the PI. The DSRB decides on the subsequent action required. The PI may be asked to submit additional information, be invited to attend a subsequent meeting, or the proposal might be sent to an independent consultant for further review. When the additional information has been obtained, the proposal is discussed at the next DSRB meeting.

d. NOT APPROVED – The proposal fails to meet one or more criteria used by the DSRB for the approval of research. Disapproval cannot be given through the expedited review mechanism and may only be given by majority vote at a convened meeting of the DSRB.

4.4.1 Appeals Against DSRB Decisions

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

a. If the DSRB determines that a study is not approve, it provides the reasons for the disapproval, in writing to the PI.

b. The PI may appeal against the DSRB's decision by responding to the DSRB Chairperson (through the DSRB Secretariat) within 30 calendar days upon receiving the outcome.

c. In the PI's appeal, he/she should include the rationale for the appeal (with supporting documents where relevant), and documentation from the Institutional Representative (IR) or designee that supports the PI's decision to appeal.

d. Upon receipt of the PI's appeal, the DSRB secretariat will forward the appeal to the REC Chairperson or designee to determine if the PI's appeal should be directed to:

    i. The same DSRB to reconsider and review its decision; or

    ii. The REC for a second initial review.

e. If the REC Chairperson or designee has determined that the PI's appeal should be directed to the same DSRB for review, then the DSRB Secretariat will add the PI's appeal to the next scheduled DSRB meeting agenda and notify the PI of the DSRB meeting date.

f. If the REC Chairperson or designee has determined that the PI's appeal should be directed to the REC for review, then the REC Secretariat will add the PI's appeal to the next scheduled REC meeting agenda. If this is more than a month away, the REC Secretariat will arrange for an ad-hoc REC meeting. The REC Secretariat will notify the PI of the REC meeting date.

g. Once the PI's appeal has been placed on the DSRB / REC agenda, the PI will be notified and will be given the opportunity to attend the meeting and present information in person. Copies of the PI's response will be provided to all members of the DSRB / REC with their regular meeting review materials.

h. If the study is directed to the REC for a second initial review, then the Chairperson of the DSRB which first reviewed the study shall not participate in the deliberation and voting, but may provide information as requested by the REC.

i. The DSRB / REC will carefully and fairly evaluate the PI's appeal in reaching its final decision. The DSRB / REC Secretariat will notify the PI of the DSRB's / REC's final decision. If the study is disapproved, this letter will include the reason(s) for the disapproval.

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

k. If the study is directed to the REC for a second initial review, then the REC Chairperson shall endorse the letter that communicates the outcome to the PI. If the study is approved, the initial reviewing DSRB shall continue to oversee and review the subsequent submissions (e.g. study amendments, UPIRTSOs etc.).

l. All PIs are encouraged to contact the DSRB to provide other types of feedback. However, other types of investigator feedback are accepted without this process.

4.5 Study Amendments

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

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

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

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

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

4.5.1 Supporting Documents for Study Amendments

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

a. A duly completed ROAM Study Amendment Cover Note (including summary and rationale of amendments);

b. Amended documents (both tracked and clean versions);

c. Any other documentation that the DSRB may specifically request; and

d. Any other relevant documentation to be given to subjects when, in the judgment of the DSRB, the additional information would add meaningfully to the protection of the rights, safety and / or well-being of the subjects.

4.5.2 Review Categories for Study Amendments

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

a. Administrative amendments – Administrative changes such as change in addresses, contacts, etc., and correction of typographical and grammatical errors fall into this category which will be reviewed and acknowledged by the DSRB Secretariat. The DSRB Secretariat will send an acknowledgment letter to the PI to indicate receipt of the administrative amendments.

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

c. Major amendments – The DSRB Secretariat will determine if the changes to the protocol affect the risk-benefit ratio of the study. Amendments that significantly affect the risk-benefit ratio will undergo a Full Board review.

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

a. Changes to the inclusion and / or exclusion criteria that significantly alter the risk-benefit ratio;

b. Major changes to the ICF or process that increases the overall risk to the participants involved in the study;

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

d. Increase in study participants for a study previously reviewed by Full Board review;

e. Alterations to the drug dose or delivery;

f. Any other type of amendment to the study that in the opinion of the DSRB should be reviewed at a Full Board meeting.

4.5.3 Applicable Fees for Study Amendments

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

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

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

4.6 Continuing Review

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

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

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

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

4.6.1 Supporting Documents for Continuing Review

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

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

b. DSMB reports or any interim analysis reports;

c. Any other documentation that the DSRB may specifically request.

4.6.2 Review Categories for Continuing Review

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

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

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

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

a. The research is permanently closed to new participants;

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

c. The research remains active only for long-term follow-up of participants.
(For a multi-centre study, the Expedited review procedure may be used by DSRB when all of the above are satisfied for NHG or partner institution sites.)

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

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

b. No additional risks have been identified.

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

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

EXPEDITED REVIEW CATEGORY 9

a. The research is not conducted under an IND or IDE;

b. The DSRB has determined and documented at a Full Board meeting that:

i. The research involves no greater than minimal risk; and

ii. No additional risks have been identified.

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

4.6.3 Study Status Reporting.

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

a. NOT YET INITIATED – No research-related activities have been performed since first approval. The PI must provide reasons for why the study has yet to be initiated.

b. ONGOING – Research-related activities are still being performed.

c. ENROLMENT CLOSED, SUBJECTS ON FOLLOW UP ONLY – The study is permanently closed to new participants, all participants have completed research-related interventions, and the research remains active only for long-term follow-up.

d. LAST PATIENT LAST VISIT OVER, DATA ANALYSIS ONGOING – There will be no more contact with participants and the remaining research activities are limited to data analysis.

e. COMPLETED – There will be no more research activities, including contact with participants or any data analysis. The PI must indicate the completion date.

f. SUSPENDED / TERMINATED –
   i. Sponsor-imposed termination / suspension: A determination from the sponsor of the study to terminate a research study or place a specific research study on hold. This determination may be made for interim data analysis, inadequate drug availability, response to a DSMB report / recommendation, or a pre-planned stopping point. The PI will be required to provide the reason for this status.

   ii. Termination / suspension by PI: A determination from the PI of the study to terminate a research study or place a specific research study on hold. This determination may be made for interim data analysis, inadequate drug availability, response to a DSMB report / recommendation, or a pre-planned stopping point. The PI will be required to provide the reason for this status.

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

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

Special Considerations for Studies with Ongoing Data Analysis

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

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

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

4.6.4 Criteria for Continuing Review

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

a. Subjects recruitment;

b. Number and reasons for withdrawal of subjects;

c. UPIRTSOs, including SAEs since the last review;

d. Expected Serious Adverse Event (SAE) for Human Biomedical Research (HBR), since last review

e. Study Amendments since the last review;

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

g. Research findings;

h. Complaints about the research;

i. Non-compliance reports,

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

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

4.7.1 Definitions

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

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

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

a. Results in or contributes to death;

b. Is life-threatening;

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation;
d. Results in or contributes to persistent or significant disability or incapacity; or

e. Results in or contributes to a congenital anomaly or birth defect.

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

4.7.2 Reportable Events

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

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

Table 16: Summary of UPIRTSO reporting requirements

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

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

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

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

Assessment of Events

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

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

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

a. The event has a reasonable temporal relationship to the intervention.

b. The event could not have been produced by the underlying disease states.

c. The event could not have been due to other non-study interventions.

d. The event follows a known pattern of response to the intervention.

e. The event disappears with cessation of intervention.

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

a. results in or contributes to death,

b. is life threatening,

c. requires inpatient hospitalisation or prolongation of existing hospitalisation,

d. results in or contributes to persistent or significant disability / incapacity,

e. results in or contributes to a congenital anomaly or birth defect, or

f. results in such other event as may be prescribed.

Examples of Reportable Events

a. Adverse event (any harm experienced by a subject regardless of whether the event was internal (on-site) or external (off-site) and regardless of whether the event meets the FDA definition of “serious adverse event”), which in the opinion of the PI are both unexpected and related.

    i. An unexpected adverse event is one, where the nature and severity of which is not consistent with information in the relevant source documents.

    ii. An adverse event is “related to the research procedures” when there are facts (evidence) or arguments to suggest a causal relationship.

b. Information that indicates a change to the risks or potential benefits of the research. For example:

    i. An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the DSRB.

    ii. A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the DSRB.

c. A breach of confidentiality.

d. Change in FDA labelling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

e. Change to the protocol taken without prior DSRB review to eliminate an apparent immediate hazard to a research subject.

f. Incarceration of a subject in a protocol not approved to enrol prisoners.

g. Event that requires prompt reporting to the sponsor.

h. Sponsor imposed suspension for risk.

i. Complaint of a subject when the complaint indicates unexpected risks or cannot be resolved by the research team.

j. Protocol violation (meaning an accidental or unintentional change to the DSRB approved protocol) that harmed subjects or others or that indicates subjects or others may be at increased risk of harm.

k. Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application], or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).

(2) Expected SAE (<u>only</u> for HBRA-regulated studies)

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

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

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

4.7.3 Reporting Timelines

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

(1) UPIRTSO

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

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

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

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

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

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

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

4.7.4 Reporting Requirements for Local Deaths in Oncology Studies

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

a. Most of such deaths occur when the subjects are in the treatment free follow-up phase (due to natural disease progression);

b. The local death(s) is / are unrelated to the investigational product;

c. The local deaths yield no clinically meaningful information that allows assessment of the risk-benefit relationship of the study,

d. There are no significant implications on the rights and welfare of the subjects.

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

Table 17: Reporting requirements for local deaths in oncology studies

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

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

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

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

For reports of deaths, the PI should supply the sponsor and the DSRB with any additional requested information (e.g. autopsy reports, medical reports, etc.).
In addition, the PI should follow any regulatory requirements related to the reporting of SAEs and USADRs to the appropriate regulatory authorities, e.g. HSA and / or MOH.

For more information on the regulatory requirements for safety reporting, please refer to the following websites:
Human Biomedical Research Act 2015, Ministry of Health Singapore, available at https://www.moh.gov.sg> Policies & Guidelines > Legislation.

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

4.8 Non-Compliances / Study Deviations

4.8.1 Definitions

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

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

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

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

a. Failure to obtain approval for research;

b. Failure to obtain renewal of approval for research;

c. Failure to obtain informed consent when required;

d. Failure to file adverse event reports;

e. Performing an unapproved research procedure;

f. Performing research at an unapproved site;

g. Failure to submit study amendments for review and approval;

h. Failure to adhere to the approved protocol;

i. Any other failure to adhere to regulations, policies and procedures related to research.

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

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

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

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

/ exclusion criteria). Like study amendments, deviations initiated by the investigator must be reviewed and approved by the DSRB and the sponsor prior to implementation, unless the change is necessary to eliminate an immediate hazard to the research subjects.

b. A study deviation is also used to refer to any other unplanned instance(s) of study non-compliance, e.g. situations in which the investigator failed to perform tests required by the protocol, or failures on the part of subjects to complete scheduled visits as required by the protocol.

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

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

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

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

a. Voluntary notification by the PI;

b. PI not responding to DSRB's queries / reminders for renewal;

c. Information given by other staff within the institution;

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

e. Monitoring reports;

f. Audit reports;

g. Complaints from research subjects.

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

4.8.3 DSRB Review of Non-Compliance Reports

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

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

Outcome of DSRB Inquiry

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

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

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

n. Mandating that the investigator attend additional training programmes;

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

p. Disqualifying the investigator from conducting any research for a period of time,

q. Other actions appropriate to the context of the non-compliance.

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

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

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

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

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

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

4.8.4 Regulatory Reporting of Serious Breaches

BREACH – Any change, divergence or departure from:

a. The principles of GCP;

b. The trial protocol agreed to by the sponsor, and approved by the IRB and HSA (as required); or

c. The clinical trial regulations.

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

a. The safety, or physical or mental integrity, of any subject of a clinical trial; or

b. The scientific value of the clinical trial.

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

a. The principles of GCP;

b. The clinical trial protocol;

c. Clinical trials regulations.

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

4.9 Changes in Study Status

4.9.1 Study Expiration and Lapses in DSRB Approval

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

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

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

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

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

4.9.2 Study Suspension / Termination

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

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

I. Study Suspension / Termination by DSRB

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

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

a. Inappropriate involvement of human subjects in research;

b. Infringement of the rights or welfare of participants;

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

d. Emergence of new information suggesting increased risk to human participants,

e. Expiry of approval.

II. Study Reactivation Following Suspension

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

a. Duration since suspension;

b. Circumstances surrounding suspension;

c. Enrolment status of the study;

d. Level of risk involved in the study; and

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

4.9.3 Study Completion

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

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

b. All participants have completed all research-related interventions.

c. Collection and analysis of individually identifiable data has been completed.

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

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

4.10 Other Notifications

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

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

a. DSMB reports;

b. Annual / interim / periodic safety reports;

c. Study insurance documentation;

d. Clinical trial agreements;

e. Interim data analyses;

f. Letters from study sponsors;

g. Any other information that the PI or sponsor wishes to notify the DSRB about.