CHAPTER 4

SUBMISSIONS TO DSRB

4.1 The Application Process

4.2 Submission of New Applications

4.3 Review of Submitted Applications

4.4 Outcome of Review

4.5 Study Amendments

4.6 Continuing Review

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

4.8 Study Deviations / Non-Compliances

4.9 Changes in Study Status

4.10 Other Study Notifications

4.1 The Application Process

4.1.1 Ethics and Compliance Online System (ECOS)

Launched on 10 May 2024, ECOS is the new IRB IT System co-developed by NHG Health and SingHealth to support research enterprise functions across the research lifecycle from Study Initiation to Completion, allowing IRBs, institutions and researchers to have a one stop oversight of research related activities.

Research applications must be submitted to the DSRB for review via ECOS at https://www.ecos-research.com.sg.

4.1.2 Timeline for Submission of Applications to DSRB

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 Research Office Checker (ROC) (if applicable) to review, DR and IR to endorse their study application(s), before the application(s) reach NHG Health DSRB by the monthly submission deadline.

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 submission timelines of other IRBs under the Mutual Recognition of IRB Reviews for Collaborative Studies, please refer to the respective IRB resource pages.

Please refer to section 4.3.1 for the different categories of review for new applications and section 4.5.2 for the different categories of review for study amendment applications

4.1.3 Endorsement by the Institution

Prior to making a submission to DSRB, investigators are required to obtain endorsements from their Research Office Checker (if applicable), DR and IR. If applicable, the submission may be reviewed by an institutional Research Office Checker before it reaches the DR and IR for endorsement.

- After the PI submission, applications are automatically routed to the DR for endorsement. If your institution has a Research Office Checker (ROC), the application will first go to the ROC for review before proceeding to the DR.

- 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.

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

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 B1 (Submission IRB and Board) of the ECOS application form. The research application will first be assigned to the domain selected by the PI but may be re-assigned to another domain based on DSRB's determination. PI may refer to Section 1.2, Role and Structure of the DSRB for the different DSRB domain specialities.

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 IRB Reviews for Collaborative Studies

With effect from 1st April 2025, IRB involving A*STAR IRB, NHG Health, NTU, NUS and SingHealth sites or their Partner Institutions, are eligible to benefit from the IRBs mutual recognition arrangement (Single IRB Review) and have their studies reviewed by 1 IRB.

To determine the appropriate reviewing IRB for collaborative studies, please refer to the Guidelines and Submission Requirements for Collaborative Studies Under Single IRB Review available on the OHRPP Research website.

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.

4.2.2 Supporting Documents Required for New Applications

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

a. A completed IRB application form;

b. Plans to compensate participants, if any;

c. Informed consent materials and assent materials (if applicable) / application for waiver of informed consent;

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

e. Questionnaires, surveys, videotapes and other such research tools (if applicable);

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

g. Investigator's Brochure or current scientific information such as basic product information brochure (e.g., summary of product characteristics (SmPC), package leaflet or labelling) and other available safety information (for all HSA regulated clinical trials);

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

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

j. Incidental Findings Management Plan;

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. Updated Curriculum Vitae (CV) of the PI and/or Co-Investigators

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

f. Any other relevant documentation 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,

g. 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) are no longer needed to be submitted to DSRB for acknowledgment / approval.

With effect from 19 October 2020, all translated documents (such as posters, flyers, brochures, patient diaries/cards, questionnaires, assessments, etc.) are no longer needed to be submitted to DSRB for approval / acknowledgment.

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.

4.2.3 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 ECOS application form.

Payment of finder's fees and / or recruitment bonuses for subject recruitment is not permitted.

The DSRB will not approve 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 out 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 informed consent materials and any other information to be provided to subject should include information regarding payment arrangements to subjects including the methods, amounts and schedule of payment. 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 timely, and not be wholly 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.

f. Reasonable reimbursement of expenses incurred by subjects, such as for travel and lodging, is not coercive.

Investigators may refer to table 10 for guidelines on payments to research participants.

Table 10: 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 and may be revised when necessary.

4.2.4 Applicable Fees for Research Applications

For studies initiated by staff from NHG Health or partner institutions, there is no direct charge for ethics review of their initial applications and any subsequent amendments.

For studies which are sponsored by the industry or commercial entities, review fees will apply for initial applications, amendment reviews and study renewals.

The review fee for study amendments is charged per submission and is not dependent on the number of documents submitted and/or changes to the DSRB application form. Payment will be waived if the study amendment only involves administrative changes (e.g., updates to version control with no change in the document content, correction of typographical errors only etc.) Determination of this would be made on a case-by-case basis by the DSRB.

The review fees for study renewals will be charged for all renewals except where the study is suspended or closed (e.g., study completion or termination). The renewal fee will be charged for reactivation of a suspended study.

Please refer to the NHG Health research website for the latest fees.

4.3 Review of Submitted Applications

4.3.1 Categories of Review

The PI should select the appropriate form type for their study in Section D1 of the ECOS Application Form:

- Application Form
  This category is for the submission of all non-Exempt (Expedited and Full Board) studies. If the study does not meet any categories under the Exemption Application Form, this should be selected.

- Exemption Application Form
  This should be selected if the study meets any of the 5 Exempt categories.

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

IV. Not Human Subjects Research

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 is 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

Research activity that falls under any of the following categories qualifies for exemption status. These studies will be reviewed by the chairperson or deputy chairperson or deputy chairperson or endorsing authority of the relevant DSRB domain.

EXEMPTION CATEGORY 1 – Normal Educational Practices and Settings

Research conducted in established or commonly accepted educational settings, that specifically involves normal educational practices, that are not likely to adversely impact students' opportunity to learn required educational content of the assessment of educators who provide instruction. Examples of such research are:

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

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

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

Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observations of public behaviour (including visual or auditory recording) if at least one of the following criteria is met:

i. The information obtained is recorded by the investigator in such a manner that the identity of human subjects cannot readily be ascertained directly or through identifiers linked to the subjects or;

ii. Any disclosure of the human subjects' responses outside of the research would not reasonably place participants at risk of psychological harm or criminal or civil liability or be damaging to the participants' financial standing, employability, educational advancement or reputation; or

iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review to determine adequate provisions to protect the privacy of the subjects and to maintain the confidentiality of data are in place.

If research includes children, only observation of public behaviour and educational tests without investigators' intervention is permitted. Education tests, surveys, and interviews with investigators involvement as well as conditions listed above (point iii) may not be applied to children.

EXEMPTION CATEGORY 3 – Benign Behavioural Interventions

Research involving benign behavioural interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

a. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot be readily be ascertained, directly or through identifiers linked to the subjects; or

b. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of psychological harm or criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement or reputation; or

c. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review to determine adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data are in place.

A. For the purpose of this provision, benign behavioural interventions are brief in duration, harmless, painless, not physical invasive, not likely to have a significant adverse lasting

impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioural interventions would include having the participants play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

B. If the research involves deceiving the subjects regarding the nature or purpose of the research, this exemption is not applicable unless the subject authorises the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

EXEMPTION CATEGORY 4 – Secondary research for which consent is not required

Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

i. The identifiable private information or identifiable biospecimens are publicly available; or

ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subject.

EXEMPTION CATEGORY 5 – Taste and Food Evaluation and Acceptance Studies

Taste and food quality evaluation and consumer acceptance studies:

i. If wholesome foods without additives are consumed; or

ii. 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 subjects, the PI will be informed to complete the research proposal using the 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 endorsing authority 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; or

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 be cleared / 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 11 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 11: 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.

IV. Not Human Subjects Research

Studies Involving Anonymised Data and/or Human Biological Materials (Not Human Subject Research) – Studies involving anonymised data / human biological materials (HBM) will not require review by DSRB as these studies do not meet the definition of human subject research (for the definition of human subject, refer to 1.4.1), if there is no use of identifiable private information or identifiable biospecimens, and no interactions or interventions with human participants in the study.

If submitted to DSRB, the study will receive a 'Not Human Subject Research' outcome.

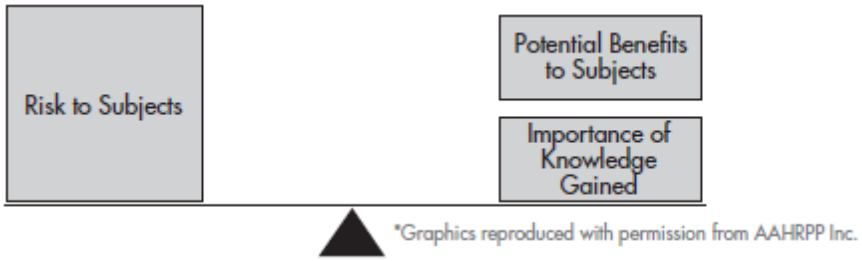
Please refer to section 1.5.2 Examples of Research-Like Activities that May Not Require DSRB Approval for more details.

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 6: 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;

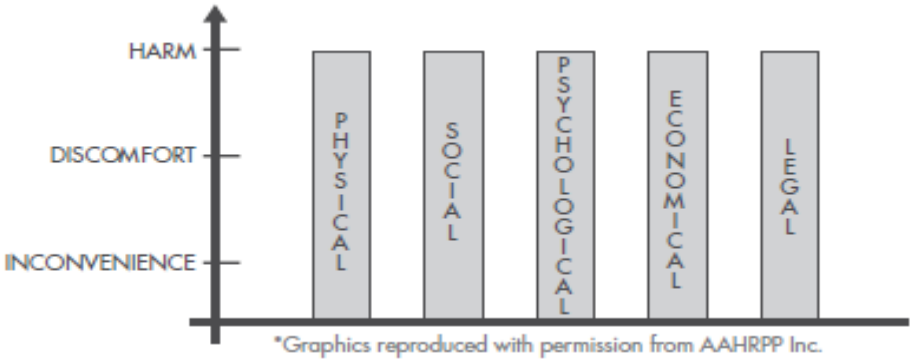
b. Psychological – e.g., psychological effects following survey asking sensitive questions;

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 7: Research-related risks

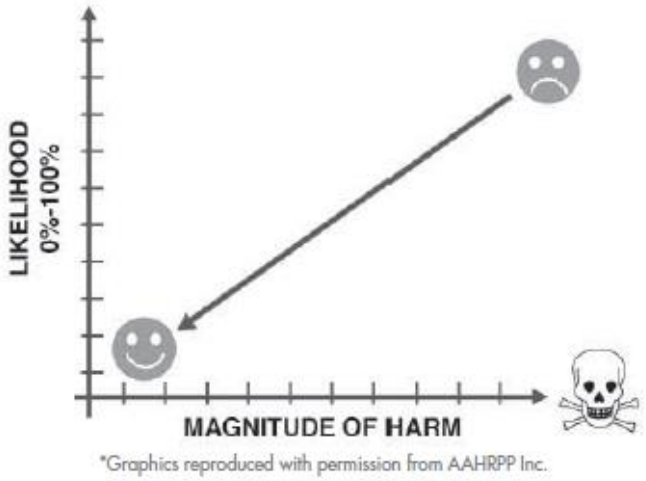


Only research-related risks should be considered, while risks associated with treatment that the subject would undergo even if not participating in the research and disease progression need not be considered while assessing research related risks.

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 8: 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 UPIRTSO / 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.

Please refer to chapter 4.7 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) and Expected Serious Adverse Event (SAE) for more information.

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, cognitively impaired 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 Vulnerable Population.

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, cognitively impaired 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.

Please refer to chapter 6.0 Research in Vulnerable Populations for more information on vulnerable subjects.

4.4 Outcome of Review

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

a. Approved

b. Not approved

c. Conditionally approved

d. Tabled for next convened meeting

e. Not Human Subjects Research

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. For proposals approved by the Full Board Review, the study is approved for a period of 1 year from the date the proposal was reviewed and approved at the meeting. For proposals reviewed by the Expedited route, the approval is for a period of 1 year from the date the proposal is reviewed by the Chairperson or designee.

b. 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.

c. 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. Upon satisfactory review, approval will be issued from the date that the requested information or materials are approved. However the expiration date of the DSRB's approval will be one year from the date the conditional approval was given. Participants must not be recruited into the study until the final approval has been issued.

   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 HUMAN SUBJECTS RESEARCH - Studies involving anonymised data / human biological materials (HBM) will not require review by DSRB as these studies do not meet the definition of human subject research (for the definition of human subject, refer to 1.4.1), if there is no use of identifiable private information or identifiable biospecimens, and no interactions or interventions with human participants in the study.

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, UPIRTSO Report (UPT) Form 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 Study Deviation / Non-Compliance (DNC) Report within 7 calendar days.

Please refer to the following for more information:

- *Chapter 3.4 Change of PI and/ or Study Team Members*
- *Chapter 4.8 Study Deviation / Non-Compliance Report*

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 ECOS Amendment Form (AMD) (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 Health 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 NHG Health Research website for the latest Applicable Fees for Research Applications.

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 Study Status Report (SSR) Form on ECOS 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 SSR (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 Health 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 Health 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 Study Status Report (SSR) 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.

Please refer to chapter 4.9 Changes in Study Status on the procedures related to changes in the status of a research study.

Special Considerations for Studies with Ongoing Data Analysis

With effect from 15 August 2018 unless otherwise determined by the DSRB, studies that have submitted a SSR 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 SSR 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 SSR 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 unfavourable medical occurrence in a research subject administered with the investigational product. The adverse event does not necessarily have a causal relationship with the treatment. For example, An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Associated with the use of the drug: There is a reasonable possibility that the experience may have been caused by the drug.

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 – Any 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 or incapacity; or

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

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

g. An important medical event that may not be immediately life-threatening or result in death or hospitalisation, that may jeopardise the participant or that may require intervention to prevent serious outcomes should be generally be considered as serious. ,

UNEXPECTED SERIOUS ADVERSE DRUG REACTION (USADR) – Any adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure or alternative documents to applicable regulatory requirements).

4.7.2 Reportable Events

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

(1) UPIRTSO – Events that are (1) unexpected and (2) related or possibly related to study must be reported to the 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 device, therapeutic product or 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 subject'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) or occurred in Singapore or outside of Singapore 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 considered to be “related to the research procedures” when there are facts (evidence) or arguments to suggest a causal relationship.

b. Unanticipated problems that involve risks to subjects or others but are not adverse:
   i. Dosing error that resulted in no detectable adverse effects during an appropriate period of careful observation.
   ii. Individually identifiable sensitive information about subjects stored on a laptop stolen, creating a potential risk of breach of confidentiality.
   iii. Incidents in the use and operation of computerised systems, which may have a significant and/or persistent impact on the research data or system security.
   iv. Investigational biologic administrative to the subjects not appropriately screened for viral contaminants including HIV and Hepatitis B causing the sexual partners of the subjects in addition to the subjects to be at risk.

c. 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.

d. A breach of confidentiality.

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

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

g. Incarceration of a participant in a protocol not approved to enrol prisoners.

h. Event that requires prompt reporting to the sponsor.

i. Sponsor imposed suspension for risk.

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

k. 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.

l. 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

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

For studies approved by other IRB(s) via mutual recognition arrangement (e.g., NHG Health 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 accurate documentation, investigation and follow-up and timely reporting of the following reportable problems to the DSRB.

(1) UPIRTSO

Table 13. 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	
Event/ Problem	All problems involving *local death	Only problems involving *local death	Life-threatening Problems not resulting in Death	All other Problems
When to Report	Regardless of causality and expectedness and causality	Must be related/ possibly related to the study and regardless of expectedness	Related/ Possibly related to the study and unexpected	

Initial Report Timeline	As soon as possible but not later than 7 calendar days after first knowledge by the investigator	Not later than 15 calendar days after first knowledge by the investigator
Follow-up Report Timeline	Within 8 calendar days of the initial report	-
***Local is defined as institution under the oversight of the NHG Health DSRB**		

(2) Expected SAE (for events occurred in Singapore and outside Singapore)

Only research studies that are regulated by the HBRA will need to be submitted to DSRB under UPIRTSO. Unexpected SAEs for HBRA studies also need to be submitted to DSRB under UPIRTSO.

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 14 below.

Table 13: 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.

4.8 Non-Compliances / Study Deviations

4.8.1 Definitions

All research conducted in institutions under the oversight of NHG Health 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 Health 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 Study Deviation / Non-Compliance to the DSRB

The DSRB encourages the reporting of study deviation / non-compliance by the PI, members of the research team or others. When a report of study deviation / non-compliance 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 DSRB may receive an allegation or a report of study deviation / non-compliance 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 study deviation / non-compliance 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 Study Deviations / Non-Compliance Reports

If the study deviation / non-compliance 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 / protocol deviation. If the PI's reply is unsatisfactory, the report will be handled as a serious or continuing study deviation / non-compliance.

If the allegation of study deviation / non-compliance 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 provided to past and/or current participants
e. Notification of current participants (required when such information may relate to participants' willingness to continue to take part in the research);

f. Require current participants to be re-consented for continued participation;

g. Modification of the continuing review schedule

h. Monitoring of the research

i. Monitoring of the consent process

j. Suspension of the research and other related studies (where applicable)

k. Termination of the research and other related studies (where applicable)

l. Notify other relevant parties to determine investigation approach or sharing of information

m. Obtaining more information pending a final decision, including the reports from investigations conducted by external parties

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

o. Mandating researcher to attend training programmes;

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

q. Disqualifying researcher from conducting any research for a period of time and/or

r. Other actions appropriate for the local context.

4.8.3.1 NHG Health Research Institution's (RI's) Review of Deviation or Non-Compliance Reports (DNC), Expected and Unexpected Serious Adverse Events (SAE)) and Notification of Reportable Events to MOH

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

The NHG Health RI reviews all deviation or non-compliances (DNCs) and expected and unexpected Serious Adverse Events (SAEs) from Human Biomedical Research (HBR) Studies reported by NHG Health researchers via ECOS.

The DNCs will be reviewed by the Principal Person-In-Charge (PIC) to determine if they are reportable to MOH.

For reportable DNCs that the PIC assesses to have **caused harm** or **had the potential to cause harm to the subject**, they must be submitted to MOH as a Suspected Offence or Contravention (SOC) **not more than seven (7) calendar days** from the time it is first made aware of the event.

For reportable DNCs that the PIC assesses to have caused **no harm** and had **no potential to cause harm** to the subject, they will be submitted to MOH as a Tiered SOC **during the annual Declaration of Compliance exercise in March/ April**.

For unexpected and related SAEs, **death and life-threatening events**, they must be reported to MOH **not more than seven (7) calendar days** from the time the RI is first made aware of the event. Any additional relevant information about the event should be recorded and submitted to MOH within eight (8) days after the record is made.

For unexpected and related SAEs that **does not result in death and is not life threatening**, the events must be reported to MOH **not more than fifteen (15) calendar days** from the time it is first made aware of the event.

For expected and related SAEs, the PIC will be informed of such events. No reporting to MOH is required.

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.

Please refer to the Guidance on Notification of Serious Breach on HSA's website for more information.

4.9 Changes in Study Status

4.9.1 Study Expiration and Lapses in DSRB Approval

The expiry date is considered to be the last date that the protocol is approved and the study cannot continue beyond thet expiry date until approval is renewed by the DSRB.

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 on ECOS, the Study Status Report (SSR) Form for continuing review well before the expiration date, allowing ample time for DSRB review.

If the PI fails to submit the SSR for an active research project, or if the DSRB has not reviewed and approved the submitted SSR 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 Study Deviation / Non-Compliance Report on ECOS to document the activities conducted during the lapse and provide an explanation for the non-compliance.

Please refer to chapter 4.8 Non-Compliances / Protocol Deviations for more information.

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 via the SSR to the DSRB within 7 days, on the ECOS System.

I. Study Suspension / Termination by DSRB

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

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

a. Inappropriate involvement of human subjects in research;

b. Infringement of the rights or welfare of participants;

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

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

e. Expiry of approval.

II. Study Reactivation Following Suspension

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

a. Duration since suspension;

b. Circumstances surrounding suspension;

c. Enrolment status of the study;

d. Level of risk involved in the study; and

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

4.9.3 Study Completion

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

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

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

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

When a study is completed, the PI should submit a study completion report within 30 days after completion of the study. Completion reports should be submitted on ECOS using the SSR.

The DSRB Secretariat will review the SSR 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 Study Notifications

Miscellaneous documents relevant to the study that do not require IRB approval may be submitted to the DSRB for acknowledgement using the Other Study Notifications (OSN) Form on the ECOS System.

Some examples of other study notifications include (but are not limited to):

a. DSMB reports;

b. Annual / interim / periodic safety reports;

c. Interim data analyses;

d. Letters from study sponsors;

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