IHH Healthcare

PIEC
PARKWAY INDEPENDENT ETHICS COMMITTEE

Parkway Independent Ethics Committee (PIEC)

Investigator Manual

Edition 7.0: Feb 2025

Contact Information

Parkway Independent Ethics Committee
(c/o Parkway Hospitals Singapore Pte Ltd)

Main Telephone: 6277 8272 **Email:** piec@ihhhealthcare.com

Dear Readers,

PIEC is established and empowered under the auspices of Parkway Hospitals Singapore Pte. Ltd. (PHSPL), whose authority applies to all research involving human subjects conducted in the institution that appoints it.

PIEC upholds the highest ethical, scientific, regulatory and professional standards of human subjects research programs, guided by and complying with the internationally-accepted standards.

This manual is intended to assist you in getting familiarized with PIEC submission requirements. We recommend that sponsors, investigators and all members of study team who will be involved in human research studies to read and understand the information in this manual.

If you need additional assistance, please do not hesitate to contact us at piec@parkwaypantai.com or 6277 8272.

Yours faithfully,
PIEC Secretariat

Table of Contents

A. Before Study Start-up

A1. What is considered research?

- A1.1 Defining Research
- A1.2 Determination of Research Status
- A1.3 What is the meaning of "engaged in research"

A1. What is considered research?

A1.1 Defining Research

Activities that involve **systematic investigation**, including research development, testing and evaluation, and are designed primarily to develop or contribute to **generalizable knowledge** are considered research.

Human Biomedical Research

Biomedical Research refers to any research done for the ultimate purpose of studying, diagnosing, treating or preventing, any disease, injury, disorder, or condition of the human mind or body, and which entails the involvements of humans, human biological materials or information derived from humans or human biological materials. Also included is research on human physiological processes.

Meaning of human biomedical research under **Human Biomedical Research Act**:

Any research that is intended to study —

i. the prevention, prognostication, diagnosis or alleviation of any disease, disorder or injury affecting the human body;

ii. the restoration, maintenance or promotion of the aesthetic appearance of human individuals through clinical procedures or techniques; or

iii. the performance or endurance of human individuals,

where the research involves —

i. subjecting an individual to any intervention (including any wilful act or omission) that has a physical, mental or physiological effect (whether temporary or permanent) on the body of the individual;

ii. the use of any individually-identifiable human biological material; or

iii. the use of any individually-identifiable health information.

Any research that involves —

i. human gametes or human embryos;

ii. cytoplasmic hybrid embryos;

iii. the introduction of any human-animal combination embryo into an animal or a human;

iv. the introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into an animal at any stage of development (including a prenatal animal foetus or animal embryo); or

v. any entity created as a result of any process referred to in paragraph (iii) and (iv).

Appointment of PIEC by Research Institution under HBRA

For research regulated under the Human Biomedical Research Act, PIEC only conducts ethics reviews on these research proposals of researchers who come under the supervision and control of research institution that formally appoints PIEC as the reviewing IRB in writing.

A research institution, in this regard, is referring to an organisation that has notified MOH of its operation as a research institution, as prescribed by the Act. Subsequently, an annual declaration of compliance is to be submitted as long as it continues operating as a research institution.

Applicant may write to us for more information on the process of appointing PIEC as the reviewing IRB for the proposed HBR.

The meaning of 'identifiable'

Individually-identifiable means the identity of the subjects is or may readily be ascertained by the investigator or associated with the information collected about the individuals.

Information is considered identifiable if any of the following are present:

- Subject Name
- Address - Street
- Address - Postal Code
- Elements of Dates (except year) related to a subject. For example, date of birth, admission or discharge dates, date of death
- Telephone Number
- Fax Number
- Electronic Mail Address
- NRIC Number
- Medical Record Numbers
- Health Plan Beneficiary Numbers
- Account Numbers
- Certificate/License Numbers
- Vehicle Identification Number and Serial Numbers Including License Plate
- Medical Device Identifiers and Serial Numbers
- Web URLs
- Internet Protocol (IP) Address
- Biometric Identifiers (finger and voice prints)
- Full Face Photographic Images
- Any Unique Identifying Number, Characteristic or Code Link to Identifier (code)

A1.2 Determination of Research Status

It is generally accepted that any activity which includes a systematic design, using a scientific approach or protocol for the purpose of drawing conclusions, and which could add to generalizable knowledge in a particular area, constitutes research. Some examples of human research are clinical trials, epidemiological research, retrospective medical records review research, human genetic research, public health research etc.

When in doubt whether an activity requires ethics review and approval, the investigator may write to the PIEC with a summary of the proposal. The PIEC will review the information and make a determination whether or not the described activity meets the definition of research. The PIEC will send a written notification to the investigator with the final determination.

A1.3 What is the meaning of "engaged in research"

PIEC considers an institution "engaged" in human subjects research when its employees or agents, for the purposes of a research project, obtain:
a. Data about the subjects of the research through intervention or interaction with them;
b. Identifiable private information about the subjects of the research; or
c. The informed consent of human subjects.

*Commercial medical services are excluded from the above. E.g. Radiology, Nuclear Med imaging, local labs etc.

A2. What are the current regulatory framework governing research reviewed and approved by PIEC?

A2. What are the current regulatory framework governing research reviewed and approved by PIEC?

The PIEC is constituted and operates in accordance with the ICH GCP, the Standard Operating Procedures for PIEC and all applicable laws and regulations.
The PIEC requirements are also in line with the Bioethics Advisory Committee recommendations outlined in the Ethics Guidelines for Human Biomedical Research, June 2015.

All research reviewed and approved by the PIEC must comply with PIEC requirements and other standards/guidelines/applicable regulations such as:

1. The Nuremberg Code
2. Declaration of Helsinki
3. Belmont Report
4. International Conference on Harmonisation Good Clinical Practice Standards (ICH GCP)
5. Medicines (Clinical Trials) Regulations and Medicines (Medicinal Products as Clinical Research Materials) Regulations
6. Health Products (Clinical Trials) Regulations and Health Products (Therapeutic Products as Clinical Research Materials) Regulations
7. Health Products (Medical Devices) (Amendment) Regulations
8. Human Biomedical Research Act
9. Human Biomedical Research Regulations
10. Personal Data Protection Act
11. DHHS Regulations 45 CFR 46 – applicable for all research funded by US Federal Funds e.g. funded by NIH, NCI, NIAIDS etc.
12. FDA Regulations 21 CFR 56, 21 CFR 50 – applicable for all research conducted under an IND or IDE or when the results of research are intended to be submitted to FDA.

The investigator must ascertain which regulations are applicable.

A3. What are the types of approval required before a research study can be initiated?

A3. What are the types of approval required before a research study can be initiated?

Ethics Approval

- Ethics approval is required for all research studies that are conducted with direct or indirect human subject participation, both funded and non-funded, to ensure protection of the rights, safety and welfare of research subjects.
- A human subject is defined as "A living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information, including, biological samples.

Regulatory Approval

- Clinical trials involving medicinal or health products require a CTC (Clinical Trial Certificate) or CTA (Clinical Trial Authorization) or CTN (Clinical Trial Notification) from the Health Sciences Authority, unless the Health Sciences Authority has given a written notification that such approval is not required. It is the responsibility of the investigator conducting the human research study to ensure that all necessary approvals have been obtained before initiating the study.
- Restricted human biomedical research should be carried out only under, and in accordance with the conditions of approval obtained from the Ministry of Health (MOH). "restricted human biomedical research" means any human biomedical research specified in the Fourth Schedule of the Human Biomedical Research Act 2015.

Institutional Approval

- It is the responsibility of the investigator to ensure that all necessary approvals at the institutional level have been obtained before initiating the study.
- For example, the investigator is conducting a research study involving inpatient stay in a hospital, the investigator must have obtained the permission from the hospital management to conduct the research study in the ward, prior to the inclusion of the hospital as one of the study sites.

A4. What are the minimum qualifications and training for the study team?

- A4.1 Definition of roles
- A4.2 Minimum qualifications
- A4.3 Minimum training requirement

A4. What are the minimum qualifications and training for the study team?

A4.1 Definition of Roles

Principal Investigator (for single-centre study)

- The person who is overall responsible for the conduct of the clinical trial at a trial site. He/She may have a team of co-investigators and/or collaborators who are assisting him in the conduct of the trial at the same trial site.

Coordinating PI (for multi-centre study)

- The lead or overall Principal Investigator assigned the responsibility for the coordination of investigators at different local study sites participating in a multi-centre trial under the oversight of PIEC.

Site PI (for multi-centre study)

- The principal investigator who is responsible for the conduct of the clinical trial at one of the local study sites participating in a multi-centre trial under the oversight of PIEC.
- Clinics/Research Centers of different branches (under the same parent company) are considered different sites. Each site must have a Site-PI.

Co-investigator

- An individual member of the study team who is designated and is under the direct supervision of the Principal Investigator/Site PI at the study site to perform research-related procedures and/or to make important research-related decisions.

Collaborator

- An individual (e.g. associates, residents, research fellows, consultants,) who is not under the direct supervision of the study site. Typically, a collaborator who does not have direct interventions/interactions with subjects or handle identifiable subject data need not submit to PIEC for approval of his/her participation. PIEC's approval is only required for collaborators who have any of the following responsibilities, but not limited to:

- Performing intervention or having interaction with subjects
- Obtaining and/or handling identifiable research data about the subjects
- Any other type of activities that in the opinion of the Chairperson should be reviewed by PIEC

A4.2 Minimum Qualification

All investigators and collaborators should possess appropriate and adequate qualifications in order to understand research proposal and conduct the research as described in the proposal.

All investigators and collaborators should submit their up-to-date curriculum vitae to PIEC as evidence of such qualifications.

For studies involving no more than minimal risk relating to biomedical research, the PI should at least be a:

a. Local registered medical practitioner, or
b. Local registered nurse, or
c. Healthcare Professional e.g. physiotherapist, audiologist, nutritionist, optometrist
d. Scientific Researcher with at least a Ph.D.

The above minimum qualification is not applicable for non-biomedical research. The PIEC will assess on a case by case basis if the investigator(s) are qualified by education, training and experience to assume responsibility for the proper conduct of the study. Non-biomedical research studies refers to those not within the scope of direct and indirect human biomedical research according to the BAC guidelines (Section 1.1 Defining Research).

For studies involving more than minimal risk, the qualification requirement of the investigator will depend on the type of trials.

a. For trials involving drug, the investigator has to be a local registered medical practitioner.
b. For trials involving medical device, the investigator has to be adequately trained to operate/use the device by submitting relevant proof of qualification to PIEC. e.g. CV and certificate of competence.
   For medical device classified as Class C and D by HSA, the principal investigator should be a local fully registered medical practitioner.

Change of Principal Investigator / Study Team Members

If the Principal Investigator is going away for an extended duration of time (3 months or more), the study should be formally transferred to another Investigator. This Investigator assumes all the responsibilities of the Principal Investigator for the conduct of the research project until the original Principal Investigator returns. This change should be reviewed and approved by the PIEC and HSA.

For new addition or change in the study team member (i.e. Co-investigator or new Site Principal Investigator), the Principal Investigator must submit a Study Amendment Cover Note, along with the curriculum vitae, all relevant training records and Annex B – Conflict of Interest Declaration Form of the new member to PIEC for approval.

A4.3 Minimum Training Requirement

All investigators must fulfil one of the following training requirements depending on the type of study submitted.

1. Human Subject Research (HSR) Course by Collaborative Institutional Training Initiative (CITI) - Social-Behavioral-Educational (SBE) or Biomedical (Biomed).

2. Good Clinical Practice (GCP) Course by Collaborative Institutional Training Initiative (CITI).

3. Other Good Clinical Practice (GCP) course: Must meet the minimum criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate Biopharma as necessary to enable mutual recognition of GCP training among trial sponsors. A list of GCP Training Solutions meeting the minimum criteria is maintained on TransCelerate's website.

A5. What are the responsibilities of a Principal Investigator?

- A5.1 Declaration of Conflict of Interest to PIEC

A5. What are the responsibilities of a Principal Investigator?

The Principal Investigator (PI) is the person responsible for the conduct of a research study at a study site.

The PI (including the Coordinating PI and the Site-PI) assumes the ultimate responsibility in ensuring that the information provided in the PIEC application form is correct and declares the following upon signing of the form:

a. He/She will not initiate the study until he /she receives written notification of the PIEC approval and the regulatory authority approval (if applicable).
b. He/She will not initiate any change in protocol without prior written approval from the PIEC except when it is necessary to reduce or eliminate immediate risk to the study participant. Thereafter, he/she will submit the proposed amendment to the PIEC and other relevant authority for approval.
c. He/She will promptly report any unanticipated problems involving risks to subjects or others (UPIRTSO) that may occur in the course of the study.
d. He/She will maintain all relevant documents and recognize that the PIEC staff and other regulatory authorities may inspect these records.
e. He/She understands that failure to comply with all applicable regulations, institutional and PIEC policies and requirements may result in the suspension or termination of this study.
f. He/She declares that there are no conflicting interests for any of the research personnel participating in the research study.
g. He/She declares that he/she has not been involved in any study that is suspended / terminated by an IRB or regulatory authority due to misconduct / non-compliance.

All investigators (including the co-Investigator(s), if any) must refer to the ICH Good Clinical Practice for their roles and responsibilities for conducting a research study in PIEC-governed sites. The PI must be fully aware of his/her responsibilities and he/she is the ultimate responsible person to ensure the study team is conducting the study in compliance with the GCP and the PIEC policies.

A5.1 Declaration of Conflict of Interest to PIEC

Financial interests are not prohibited, and not all financial interests cause conflicts of interest or affect the rights and welfare of human subjects. PIEC recognizes the complexity of the relationships between government, academia, industry and others, and recognizes that these relationships often legitimately include financial relationships. However, to the extent to which financial interests may affect the rights and welfare of human subjects in research, IRBs, institutions, and investigators need to consider what actions regarding financial interests may be necessary to protect those subjects from bias in judgment as a result of conflict of interest.

Ethical conduct of a research study requires both disclosures and effective management of conflict of interest.

Definitions	
Conflicting Interest	A conflicting interest can be broadly defined to refer to any interest of the investigator or his/her immediate family (includes spouse and each dependent child) that competes with the investigator's obligation to protect the rights and welfare of research subjects.
Financial Interest	Significant financial interest means anything of monetary value, including but not limited to, salary or payments for services (e.g., consulting fees or honoraria); equity interests (e.g. Stocks, stock options or other ownership interests); intellectual property rights (e.g., patents, copyrights and royalties from such rights), and board or executive relationships.

Sources of conflict of interest are listed below, but not limited to:

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

Payments (e.g. salary, consultation fees, honoraria for serving on advisory board or for giving lectures) from any company that may benefit from the research activity.

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

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

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

Any **incentive** connected with subject recruitment or completion of research study (e.g. finder's fee, recruitment bonuses etc.)

Conflict of interest exists when an investigator's judgment concerning a primary interest (eg subject's welfare, integrity of research) may be biased by a secondary interest (eg personal gain).

Each research personnel (including the investigator(s), research nurse or study coordinator etc.) must complete the PIEC Application Form Annex B – Conflict of Interest Declaration Form. The Principal Investigator assumes the responsibility to ensure that all research personnel in the study will make such declaration at the time of submission or as and when there is change in research personnel or conflict of interest becomes existent during the course of the study.

When conflict of interest exists, the affected research personnel / the principal investigator shall propose management strategies that aim at eliminating and minimizing the impact of conflict of interest for PIEC's consideration.

B. Submission Process for Ethics Approval

B1. What is the application process?

B1. What is the application process?

The PIEC relies on the documentation submitted by Investigators for initial and continuing review. Therefore, the material submitted must provide PIEC with enough information about a study to assess if it adequately meets the PIEC's criteria for approval.

A submitted research proposal will be scheduled for PIEC review only when the PIEC Secretariat has determined that the information and materials submitted provide an adequate description of the proposed research.

Submission Requirement
Effective 01 January 2022, all applicants are required to make electronic submission to PIEC via email/ Sharepoint for all types of submissions. All applicants have to endorse the application using electronic signature by AdobeSign/ DocuSign only.
Note: Scanned/ Inserted image of signature is not acceptable.

Please email piec@parkwaypantai.com with the following details for access to Sharepoint (for new applications):

- Study title
- Protocol number (if any)
- Billing details (company to bill, billing address, contact person, email & telephone number). Include PO number, if applicable

Applicants must obtain the latest forms and information on submission deadlines and review fees on our website https://www.ihhhealthcare.com/healthcare-professionals/ethics-committee/resources and are responsible to ensure that the latest forms are used in their submission.

Submission Deadline

The submission deadline for each month's Full Board Review is updated on a yearly basis. Applications received after the deadline may only be reviewed in the next Full Board Review. There is no Full Board Review Meeting in the month of December.

Please refer to our meeting schedule here
https://www.ihhhealthcare.com/healthcare-professionals/ethics-committee/meeting-schedule

Submissions that require expedited / exemption review may be submitted to the PIEC on any working days via email/Sharepoint.

Review Fees:

Payment should be made to "Parkway Hospitals Singapore Pte Ltd" via bank transfer (indicate the protocol number or PIEC Ref number)

Refer to the bank details published on our website:
https://www.ihhhealthcare.com/healthcare-professionals/ethics-committee/fee-structure

**Please note that the PIEC will be unable to release the approval letters if payment has not been received.*

B2. Full Board Review, Expedited Review and Exemption Review

- B2.1 Full Board Review
- B2.2 Expedited Review
- B2.3 Exemption from Review

B2. Full Board Review, Expedited Review and Exemption Review

B2.1 Full Board Review

All research proposals that do not qualify for Exemption or Expedited Review category will be reviewed by the Full Board Review category.

These research proposals will be reviewed at a convened meeting held monthly, except December.

B2.2 Expedited Review

Expedited Review process may be used for:

a. Initial Review of new research proposals
b. Continuing Review
c. Review of modifications to previously approved research
d. Review of modifications stipulated by PIEC;
e. Safety reporting e.g. UPIRTSO;
f. Non-Compliance Reporting

To qualify for review by expedited process, a research proposal must meet the following criteria:

1. The research proposal presents no more than minimal risk to research subjects;
2. Identification of subjects and / or their responses does not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing, 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;
3. The research is not classified*; and
4. The research activity is listed in one of the Categories of Research listed below

The PIEC assumes full authority to escalate a study under expedited category to full board review, if deemed necessary.

**Classified Research - that bears a security classification from the federal government as top secret. Classified research restricts some or all of the results, procedures and personnel working on the project under rules established by the agency for which the research is being conducted.*

Categories of Research that qualify for expedited review:

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 labeling.

Category 2 - Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

- from healthy, non-pregnant adults who weigh at least 50 kgs. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
- from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

Category 3 - Prospective collection of biological specimens for research purposes by noninvasive means.

Examples:

- hair and nail clippings in a nondisfiguring manner;
- deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
- permanent teeth if routine patient care indicates a need for extraction;
- excreta and external secretions (including sweat);
- uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
- placenta removed at delivery;
- amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
- 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;
- mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
- sputum collected after saline mist nebulization.

Category 4 - Collection of data through noninvasive procedures (not involving general anesthesia 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:

- 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 subject or an invasion of the subject's privacy;
- weighing or testing sensory acuity;
- magnetic resonance imaging;
- electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
- Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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).

Category 6 - Collection of data from voice, video, digital, or image recordings made for research purposes.

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

B2.3 Exemption From Review

It is the responsibility of the Principal Investigator to apply for exemption from review. The investigators are not given the authority to make an independent determination that the proposed research is exempted. Only studies that have official approval from PIEC for exemption will qualify as exempted studies.

Categories of Research Qualifies for Exemption

Exemption Category 1 - Research in Established or Commonly Accepted Educational 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 or the assessment of educators who provide instruction, such as:

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.

Examples of research that are not exempt under this category:
i. Evaluation of a radically new instructional strategy
ii. Use of random assignment of subjects to different instructional methods
iii. Educational research involves deception or withholding of information from subjects
iv. Physical education involves intense exercise

Exemption Category 2 - Educational Tests, Surveys, Interviews, Observations of Public Behavior

Research that only includes interactions involvininterview procedures, or observation of public behavior (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 the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' 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 PIEC determines that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. (Note: Criteria (iii) does not apply to research involving minors.)

Examples of research that are not exempt under this category:
i. Survey research that deals with sensitive and private aspects of the subject's behavior e.g. sexual preferences, substance abuse, or illegal conduct if the data are linked to individual subjects.
ii. Surveys or cognitive/diagnostic test which are psychologically invasive (e.g. detailed personality inventory) that may cause the subject to experience emotional distress or discomfort while answering them, whether or not data are linked to individual subjects.
g educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures,

Exemption Category 3 – Benign Behavioral Interventions in Conjunction with the Collection of Information From Adult Subjects

Research involving benign behavioral 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 readily be ascertained, directly or through identifiers linked to the subjects;

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of 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 PIEC determines that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

***Benign behavioral interventions are brief in duration, harmless, painless, not physically 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.**

Examples include having the subjects 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.

Examples of research that are not exempt under this category:
Research involves deceiving the subjects regarding the nature or purposes of the research, unless the subject authorizes 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 does not require informed consent, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available;

(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 subjects;

(iii) Research use of personal data when that use is regulated by PDPA and conditions under Third Schedule to allow such use without consent are satisfied; or

(iv) The research is conducted by, or on behalf of, government using government-generated or government-collected information obtained for non-research activities for the purposes of and in accordance with application laws and regulations. For example, the use of information (including linkages from multiple databases) from any national or disease registry for epidemiological and public health research, where information may have been collected routinely by law e.g. Infectious Diseases Act, National Registry of Diseases Act or Statistics Act.

Exceptions for HBRA-regulated research:

i. *Applicant is required to apply for waiver of requirements for appropriate consent. Research is not exempt if waiver is not granted by PIEC.*
ii. *Research is not exempt if the investigators, having obtained identifiable private information or specimens from existing records or specimens, record the data or information in a coded manner, even though the investigators do not have access to the subject's identity which is linked to the data or specimen, since the code would enable subjects to be identified through identifiers linked to the subjects.*
iii. *Research is not exempt if materials are not existent ("on the shelf") at the time the research begins or use of additional research material prospectively collected after the research is initiated.*

Exemption Category 5 – Research and Demonstration Projects that Are Conducted or Supported by Government Agencies

Research and demonstration projects that are conducted or supported by government agencies or otherwise subject to the approval of government agencies, and that are designed to study, evaluate, improve or otherwise examine:

i. Public benefit or service programs, including procedures for obtaining benefits or services under those programs;
ii. Possible changes in or alternatives to those programs or procedures; or
iii. Possible changes in methods or levels of payment for benefits or services under those programs.

Such projects include, but are not limited to, internal studies by government employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants.

Exemption Category 6 – Taste and Food Quality Evaluation and Consumer 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 by the Health Sciences Authority or approved by National Environment Agency or the Agri-Food and Veterinary Authority of Singapore.

Examples of research that are not exempt under this category:

i. Consumption of any type or volume of food that has any potential risks such as indigestion or vitamin deficiencies.
ii. Consumption of alcohol, vitamin, or supplements such as protein powder, creatine, glucosamine chondroitin sulfate etc.

Exemption Category 7 – Storage or Maintenance for Secondary Use for Which Broad Consent is Required

This category is for storage or maintenance of identifiable private information or identifiable biospecimens, prior to secondary analysis, if PIEC determines that the following are satisfied:

(i) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained;
(ii) Broad consent is appropriately documented or waiver of documentation is appropriate; and
(iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Exceptions for HBRA-regulated studies:
1) Appropriate consent is obtained for the removal of human tissue from a person for use in research and/or for storing human tissue for subsequent use in research.

Exemption Category 8 – Secondary Research for Which Broad Consent is Required

Research involving the use of existing identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:
(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained;

(ii) Documentation of informed consent was appropriate or waiver of documentation of consent was obtained;

(iii) PIEC determines that
a. there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
b. the research to be conducted is within the scope of the broad consent; and

(iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

Exceptions for HBRA-regulated studies:
i. Applicant must provide documentary proof that consent to permit future research use of individually- identifiable information has been obtained.
ii. Appropriate consent is obtained for using human tissue in research.

Exemption Category 9 – Research Involving the Use of Human Cell Lines, DNAs, RNAs and Substantially Manipulated Biological Material

Research involving the use of established commercially available human cell lines, anonymous human DNAs, RNAs or substantially manipulated biological material, excluding *restricted Human Biomedical Research.

**** Restricted Human Biomedical Research is subject to full board review.***

Note: Much controversy arose on whether emerging technologies like genome sequencing alter what it means for biospecimens to be "identifiable." If at some point if PIEC decides that biospecimens are inherently identifiable, then such research will be considered Human Subjects Research

Special Considerations
The criteria for exemption do not apply for:

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

Continuing Review is not Required for Studies Exempted from Review
Exempted studies are not subjected to continuing review or any post-approval reporting requirements, unless there is any change in the protocol that affects its exemption status. The investigator must submit the modified research protocol to the PIEC for review prior to implementation of the modified research project.

The PI is required to notify PIEC when the study is completed.

B3. What are the documents needed for submission?

- B3.1 Documents for Submission
- B3.2 Informed Consent
- B3.3 Waiver or Alteration of Informed Consent Process
- B3.4 Re-consent

B3. What are the documents needed for submission?

B3.1 Documents for Submission

Submission Requirements for Initial Review (Full Board and Expedited)

Principal Investigator (PI) / Coordinating PI applying for initial review of a research proposal must submit:

I. PIEC Application Form and relevant Annexes (A-H)
- Annex A – Placebo Usage
- Annex B – Conflict of Interest Declaration Form (For all study team members and study staff)
- Annex C – Biological Materials Storage
- Annex D – Industry Sponsored Studies
- Annex E – Waiver of Informed Consent
- Annex F – Research Involving Pregnant Women, Foetuses and Neonates
- Annex G – Research Involving Children (Persons under the age of 21 years.)
- Annex H – Indemnity Form (for all study sites)

II. Study Protocol
III. Participant Information Sheet and Consent Form
IV. Investigator's Brochure or Product Inserts (for drug / device trials)
V. Recruitment materials intended to be seen or heard by potential subjects, including email solicitations, radio broadcast, newspaper advertisement, poster, letter of invitation to subjects etc (if used)
VI. Questionnaires, Surveys, Videos, Diary Card and any other such research tools (if used)
VII. Written information intended to be provided to subjects (if used)
VIII. Data Collection Form / Case Report Form
IX. Curriculum Vitae of all Investigators
X. Relevant Training Certificates / GCP certificate / CITI certificate (for all investigators)
XI. Translated Consent Document and Translation Certificates (if used)
XII. Publications / references
XIII. Certificate of Insurance (Applicable to all clinical trials)
XIV. Any other relevant documents

Additional requirements: if necessary the PIEC may require applicants to submit:

I. Financial Disclosure Statement
II. Clinical Trial Agreement for industry sponsored research
III. Documentation that the study has been disapproved by other IRBs
IV. Any other documentation that the PIEC may specifically request.
V. Any other relevant documentation to be given to subjects when, in the judgment of the PIEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects

Submission Requirements for Exemption from Review

Principal Investigator (PI) / Coordinating PI applying for exemption of a research proposal must submit:

I. PIEC Exemption Application Form
II. Study Protocol
III. If applicable, the survey form, data collection form, proof of purchase for commercial cell lines, material transfer agreement etc
IV. Consent document e.g. in the form of a subject information sheet or letter, a consent statement added to the beginning of the survey form or a detailed consent document
V. Annex B – Conflict of Interest Declaration Form (For all study team members and study staff)
VI. Annex C – Biological Materials Storage
VII. Annex D – Industry Sponsored Studies
VIII. Annex E - Waiver of Informed Consent, if applicable
IX. Annex H – Indemnity Form (for all study sites)
X. Recruitment materials intended to be seen or heard by potential subjects, including email solicitations, radio broadcast, newspaper advertisement, poster, letter of invitation to subjects etc (if used)
XI. Questionnaires, Surveys, Videos, Diary Card and any other such research tools (if used)
XII. Written information intended to be provided to subjects (if used)
XIII. Data Collection Form / Case Report Form
XIV. Curriculum Vitae of all Investigators
XV. Relevant Training Certificates / GCP certificate / CITI certificate (for all investigators)
XVI. Any other relevant documents

B3.2 Informed Consent

The Basic Principles

1. Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular research project, after having been informed of all aspects of the research study that are relevant to the subject's decision to participate. Informed consent is to be documented by means of a written, signed, and dated informed consent document.

2. In general, consent to participation must be obtained from the subject. In cases where the legally acceptable representative may be required to consent on behalf of the subject, PIEC will assess the requirement based on the subject population being studied or other special circumstances.

3. Prior to the beginning of a research or re-consenting subject of continued participation in the research, the principal investigator must have PIEC written approval of the written informed consent form and any other written information to be provided to the subjects. PIEC makes determination that the consent document embodies the basic and required additional elements of disclosure.

4. The researcher will give either the participant or the representative adequate opportunity to read the consent document before it is signed. Before informed consent may be obtained, subjects must be given ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the research. All questions about the research should be answered to the satisfaction of the subject.

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

6. Informed Consent discussion should be conducted by the Principal Investigator (PI) or a member of the research team as delegated by the PI. The person obtaining consent must be sufficiently trained and knowledgeable about the study to answer questions posed by patients. When PI delegates this important task, he/she needs to be sure that those who obtain are properly qualified and know when to refer questions that may exceed their expertise.

7. Informed consent should take place in person and the investigator or a person delegated to take consent shall fully inform subjects of all pertinent aspects of the research. For example, a process where consent document is forwarded to subjects with instructions to call back with questions, sign and mail back is not acceptable.

8. Prior to a subject's participation in a research, the written informed consent form should be signed and personally dated by the subject, or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

9. Prior to participation in a research, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During the course of a study, the subject should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

10. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally representative and the impartial witness, where applicable. A translated informed consent form shall be used, whenever appropriate.

11. Informed Consent is not a onetime event prior to enrolling research subjects, but a continuous ongoing process. Investigators must revise the informed consent form and inform subjects whenever important new information becomes available that may relevant to their willingness to continue participation in the research.

12. Neither the investigator, nor any of the research team member or research staff, should coerce or unduly influence a subject to participate or to continue participate in a research.

13. The oral and written information concerning the research must not contain any exculpatory language that causes the subject or the subject's legally acceptable representative to waive or appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

14. Investigator should inform research subjects of the opportunity to turn to PIEC for advice if they are in any way unhappy with the research.

Electronic Informed Consent

For submission purpose, applicant is required to provide the consent document and describe the eIC process.

1. Copies of consent forms (and informational materials, including any videos and Web-based presentations, which the subject will receive and view during the eIC process)
2. Any optional questions or methods used to gauge subject comprehension of key study elements.
3. If the program uses hyperlinks to convey study-related information, the contents to which subjects are referred in order to determine if the study-related information that has been supplied is accurate and appropriate.
4. Screenshots of the eICF platform / webapp.

The following aspects of the eIC process shall be described in detail in the application:

a. how eIC will be administered (e.g. eICF to be shown in a tablet or emailed to subject prior to enrolment or eIC online system will be used.
b. whether paper based ICF remains in use with an addition option of eICF or only eICF will be administered to the subjects.
c. Whether eICF will be adminsitered during a face to face or virtual session with PI and how will study team ensure a condusive environment during the informed consent process.
d. how will study team maintain the correct version of consent document on web application used for eIC.
e. Refer to GCP for the conduct of informed consent process (i.e. face to face discussion between patient and PI, ample time given to subject for decision making, condusive environment etc)
f. Specify the documentation of informed consent (method of signing ICF, filing in medical records / study files)
    - Signing using a finger/stylus on a touch screen
    - Ticking a checkbox or clicking an 'I accept' button via an electronic system that can uniquely identity the participant
    - Digital signature
g. How will signed ICF copy given to subject
h. If remote consent is used, when will is be used and study team to justify why face-to face is not possible (PIEC will review the suitability of remote consent depending on the nature of the study, purpose of consent and patient type).

Informed Consent Elements

S/N	Regulations / Guidelines	Sections
1		**STUDY INFORMATION**
1.1		A full title of the research
1.2		The name of principal investigator and name of study site
1.3		The name of the study sponsor, if any
1.4	HHS	Subjects are informed about any grant or financial incentives being provided to the researcher or the institution from the sponsor, including financial relationships or interests that are associated with the clinical investigation, such as payments for services, equity interests or intellectual property rights.
1.5	HHS	Subjects are explicitly informed of other potential conflict of interests of the research team.
2		**PURPOSE OF THE RESEARCH STUDY**
2.1	ICH-GCP 4.8.10 CT Reg 19(a) HBRA 12(1)(a) 21 CFR 50.25(a) 45 CFR 46.116(b)	A statement that the trial involves research or the investigational nature of the research
2.2	ICH-GCP 4.8.10 CT Reg 19(b) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 12(1)(b) HBRA 12(2)(a)	The purpose of the research; or The specific research purpose for which the tissue is intended to be used, if this information is available but if not available, the purpose for which the tissue is intended to be used may be stated as for general research
2.3	HBRA 12(2)(c)	<u>For adult/minor lacking mental capacity / sufficient understanding and intelligence to give consent:</u> The proposed areas of research approved by the institutional review board in a case where it has waived the requirement that the removal of the tissue is primarily for a therapeutic or diagnostic purpose.
2.4		Why participant is being invited to participate.
2.5	ICH-GCP 4.8.10 CT Reg 19(t) 21 CFR 50.25(b) 45 CFR 46.116(c)	The approximate number of subjects involved in the research (study site, Singapore and global).
2.6	ICH-GCP 4.8.10 CT Reg 19(s) 21 CFR 50.25(a) 45 CFR 46.116(b)	The expected duration of the subject's participation in the research

3		**WHAT PROCEDURES WILL BE FOLLOWED IN THIS STUDY**
3.1	ICH-GCP 4.8.10 CT Reg 19(c) FDA guidelines	The treatments or procedures to be administered in the research. To describe the test article and the control, whether the control is a medically recognized standard of care or is a placebo (including an explanation of what a placebo is).
3.2	ICH-GCP 4.8.10 CT Reg 19(c)	The probability for random assignment to each treatment or procedure.
3.3	ICH-GCP 4.8.10 CT Reg 19(d) 21 CFR 50.25(a) 45 CFR 46.116(b)	A description of visits and the procedures to be followed in the research, including all invasive procedures.
4		**WHAT WILL HAPPEN AFTER THE STUDY IS COMPLETED**
	DoH	Whether provisions is made available for post-trial access for all participants who still need an intervention identified as beneficial in the clinical trial. Note: Promising lifetime free product might become an undue inducement to participate in a trial in some clinical settings
5		WHAT IS NOT STANDARD CARE OR EXPERIMENTAL IN THIS STUDY
5.1	ICH-GCP 4.8.10 CT Reg 19(f) 21 CFR 50.25(a) 45 CFR 46.116(b)	A description of all the aspects of the study that are being done specifically for the research or identification of any procedures that are experimental. Procedures related solely to research must be explained.

6		WHAT WILL HAPPEN TO DATA / IMAGES / BIOSPECIMEN TAKEN FOR RESEARCH
6.1	45 CFR 46.116(b) HBRA 12(1)(k) HBRA 12(2)(m)	Whether research involves the collection of identifiable private information or identifiable biospecimens; Whether the participation of the research subject involves information in individually-identifiable form; Whether the tissue donation would result in the use of the donor's tissue in an individually-identifiable form.
6.2	HBRA 12(2)(b)	Whether the tissue will be used for any purpose other than research and if so, the specific purpose for which the tissue will be used;
6.3	HBRA 12(2)(n)	Whether the tissue will be used in restricted human biomedical research involving human-animal combinations;
6.4	CT Reg 19(1)(ta) HBRA 12(2)(q)	Whether the tissue will be exported or removed from Singapore to a place outside Singapore;
6.5	HBRA 12(1)(j) HBRA 12(2)(k)	Where applicable, whether biological material taken from the research subject will be destroyed, discarded or stored for future research.
6.6	45 CFR 46.116(b) HBRA 12(1)(i) HBRA 12(2)(j)	Whether individually-identifiable information obtained from the research subject/tissue donor will be used for future research. E.g. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens: A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.
6.7	45 CFR 46.116(c) CT Reg 19(1)(ta) HBRA 12(2)(e)	A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit. The donation of the tissue is voluntary and the renunciation of the donor's rights to the tissue and any intellectual property rights that may be derived from the use of the tissue;
6.8	45 CFR 46.116(c)	For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (that is, sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).
6.9	45 CFR 46.116(c)	A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
6.10	CT Reg 19(1)(ta) HBRA 12(1)(m) HBRA 12(2)(o)	Whether the research subject / the donor of human tissue / the person authorised to give consent, would wish to be re-identified in the case of an incidental finding relating to the collected tissue if the research expressly provides for such re-identification.

7		**RESPONSIBILITIES OF THE SUBJECTS**
7.1	ICH-GCP 4.8.10 CT Reg 19(e) 21 CFR 50.25(a)	A description of responsibilities of the subject. E.g. attend clinic visits, maintenance of diaries, and medical or dietary restrictions (including the need to avoid specific medications or activities, such as participation in other clinical investigations).
8		**POSSIBLE RISKS AND SIDE EFFECTS**
8.1	ICH-GCP 4.8.10 CT Reg 19(g) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 12(1)(c) HBRA 12(2)(d)	A description of any reasonably foreseeable risks, discomforts or inconveniences to the subject and, where applicable, to any embryo, foetus or nursing infant, arising from the research/trial or from the removal of the tissue. This includes risks or discomforts of tests, interventions and procedures required by the protocol (including standard medical procedures, exams and tests), especially those that carry significant risk of morbidity or mortality, possible risks or discomforts due to changes to a subject's medical care (e.g., by changing the subject's stable medication regimen or by randomizing to placebo), the explanation of potential risks of the test article and control.
8.2	21 CFR 50.25(b) 45 CFR 46.116(c)	A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) or to a nursing infant, which are currently unforeseeable.
8.3		A description of risk in breach of confidentiality / genetic discrimination etc, if applicable
9		**POSSIBLE BENEFITS FROM PARTICIPATION IN THE STUDY**
9.1	ICH-GCP 4.8.10 CT Reg 19(h) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 12(1)(d)	A description of any benefits to the subject or to others that may reasonably be expected from the research, including whether there is any intended clinical benefit to the subject;
9.2	ICH-GCP 4.8.10	When there is no intended clinical benefit to the subject, the subject should be made aware of this.
10		**ALTERNATIVES TO PARTICIPATION**
10.1	ICH-GCP 4.8.10 CT Reg 19(i) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 12(1)(e): Situational	Where applicable, a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, and their important potential benefits and risks of such alternatives.
11		**COSTS AND PAYMENTS RELATED TO PARTICIPATION IN THE STUDY**
11.1	ICH-GCP 3.1.9 CT Reg 19(k)	All information concerning payment to the subject for participating in the trial, including: - the methods, amount and schedule of payments, - the circumstances which may result in the pro-ration of payment to the subject for participating in the trial;
11.2	ICH-GCP 4.8.10 CT Reg 19(l) 21 CFR 50.25(b) 45 CFR 46.116(c) HBRA 12(1)(g): Situational HBRA 12(2)(h)	Any anticipated expenses the subject is likely to incur as a consequence of participating in the research or donating tissue.

12		**VOLUNTARY PARTICIPATION**
12.1	ICH-GCP 4.8.10 CT Reg 19(m) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 14(1) HBRA 12(1)(n) HBRA 12(2)(f)	Assurance that participation is voluntary; It is the research subject's / donor's right that he/she may, at any time, withdraw the consent to the subject's participation in the human biomedical research.
12.2	ICH-GCP 4.8.10 CT Reg 19(m) 21 CFR 50.25(a) 45 CFR 46.116(b)	A statement that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled.
12.3	ICH-GCP 4.8.10 CT Reg 19(m) 21 CFR 50.25(a) 45 CFR 46.116(b)	A statement that the participant can discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
12.4	ICH-GCP 4.8.10 CT Reg 19(p) 21 CFR 50.25(b) 45 CFR 46.116(c)	Subject or subject's legal representative (including subject who regains capacity to consent and family member contacted for a subject in a clinical trial in an emergency situation) will be informed in a timely manner of any information which becomes available and which may be relevant to the decision of the potential subject being, or the subject continuing to be, a subject (as the case may be);
12.5	HBRA 12(1)(l) HBRA 12(2)(l)	The circumstances, if any, under which, the research subject or the person authorised to give consent will be contacted for further consent, including but not limited to changes in the proposed research, serious adverse events that would lead to a change in the proposed research, the development of capacity by minors to make decisions and any other circumstances which could be specific to a particular research proposal; and/or Whether, and the circumstances under which, the donor or the person authorised to give consent under this Part, as the case may be, will be contacted for further consent;
12.6	ICH-GCP 4.8.10 CT Reg 19(r) 21 CFR 50.25(b) 45 CFR 46.116(c)	Anticipated circumstances under which the subject's participation may be terminated by the researcher without regard to the subject's or legally authorized representative's consent.
12.7	21 CFR 50.25(b) 45 CFR 46.116(c) HBRA 12(1)(n)	The consequences of a subject's decision to withdraw from the research, the limitations of such withdrawal* and procedures for orderly termination of participation by the subject. * The tissue is individually-identifiable and has not been used for the research; or the tissue is individually-identifiable and has been used for the research but it is practicable to discontinue further use of the tissue for the research. The withdrawal of consent does not affect the research information obtained before the consent is withdrawn and such information may be retained and used for the research.

13		**COMPENSATION FOR INJURY**
13.1	ICH-GCP 4.8.10 CT Reg 19(j) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 12(1)(f): Situational HBRA 12(2)(g)	An explanation as to whether any compensation and/or medical treatments are available if injury occurs (arising from participation in the research or in the process of tissue donation) and, if so, what they consist of, or where further information may be obtained. If no compensation is available, the consent process should include statements such as and that subject is not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.
14		**CONFIDENTIALITY OF STUDY AND MEDICAL RECORDS**
14.1	ICH-GCP 4.8.10 CT Reg 19(o) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 12(1)(h) HBAR 12(2)(i)	A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. E.g. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.
14.2	ICH-GCP 4.8.10 CT Reg 19(n) 21 CFR 50.25(a) 45 CFR 46.116(b)	The persons who will be granted access to the subject's medical records and the extent of such access, including the possibility that the Authority may inspect the records; e.g. the monitor(s), the auditor(s), the health authorities (FDA, HSA) and the ethics committee, and the Ministry of Health will be granted direct access to the subject's original medical records for verification of research procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations.
14.3	ICH-GCP 4.8.10 CT Reg 19(n)	By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access
14.4	ICH-GCP 4.8.10 21 CFR 50.25(c)	If the results of the trial are published, the subject's identity will remain confidential. For FDA Trials: A description of this clinical trial will be available http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
14.5		When appropriate, in the event the research involves tests such as HIV testing, that require mandatory reporting to the Ministry of Health, if result is positive.
14.6		Retention period of study records by study sites (for example, 15 years after trial completion or according to sponsor's requirement, whichever longer)

15		**CONTACT INFORMATION**
15.1	ICH-GCP 4.8.10 CT Reg 19(q) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 12(1)(o) HBRA 12(2)(p)	An explanation of whom to contact (and contact details) for answers to pertinent questions about the research or to obtain further information on the purposes for which the tissue will be used.
15.2	ICH-GCP 4.8.10 CT Reg 19(q) 21 CFR 50.25(a) 45 CFR 46.116(b) HBRA 12(1)(o) HBRA 12(2)(p)	An explanation of whom to contact (and contact details) for answers to pertinent questions about the rights of subjects or to provide feedback in relation to the biomedical research or purposes for which the tissue will be used.
15.3	ICH-GCP 4.8.10 CT Reg 19(q) 21 CFR 50.25(a) 45 CFR 46.116(b)	An explanation of whom to contact (and contact details) in the event of research-related injury to the subject.
16		**SIGNATURE**
16.1		Provision for Subject (or Next of Kin of deceased subject) to sign and date
16.2		Provision of Legally Acceptable Representative to sign and date (Research must be reviewed and approved to include minors or persons lacking mental capacity)
16.3		Provision for impartial witness / witness to sign and date - If the person giving the consent is unable to sign or date personally in writing - If the person giving the consent is unable to read/illiterate - For all HBRA-regulated research (witness need not be impartial)
16.4		Provision for person obtaining consent to sign and date
16.5	21 CFR 50.27(a)	A copy shall be given to the person signing the form.

Surrogate Consent

A legally acceptable representative (LAR) may give consent on behalf of the individual for participation in a research only when the individual does not have the capacity to give legally effective informed consent, such as:

i. Minor
ii. Fetus
iii. Person who lacks mental capacity / who is unconscious

Special Considerations - Subjects who are unable to read

1. When a subject or a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.
2. The written informed consent document and any other written information to be provided to the subjects, should be read and explained to the subject or the subject's legally acceptable representative.
3. The subject or the subject's legally acceptable representative must orally consent to the subject's participation in the research and, if capable of doing so, the subject should sign and personally date the informed consent document.
4. The witness should sign and personally date the consent document after all of the above have been fulfilled. By signing the consent document, the witness attests that:
    i. The information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and
    ii. The informed consent was freely given by the subject or the subject's legally acceptable representative.
5. Impartial witness should be instructed about the circumstances under which they should decline to sign the informed consent form, e.g. if the witness observe any indication of coercion by the investigator or study team or lack of understanding on the part of subject.

Special Considerations - Non-English Speaking Subjects

1. It is not acceptable to exclude potential subjects based on their inability to speak and understand English.
2. The written consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. A certified translation of the informed consent document must be submitted to PIEC for review prior to use. PIEC strongly encourages the use of this procedure whenever possible.

B3.3 Waiver or Alteration of Informed Consent Process

Waiver of consent or alteration of informed consent process shall be requested by the investigator and justifications of the request must be included in the ethics application (Annex E – Waiver of Informed Consent).

In a request for waiver of informed consent, the study team is required to provide justifications/evidence that:

i. The research involves no more than minimal risk to the subjects;
ii. The research could not practicably be carried out without the requested waiver or alteration.
iii. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
iv. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
v. The process of obtaining consent from the person, to which the individually-identifiable human biological material or health information relates, will involve a disproportionate amount of effort and resources relative to the research requirements;
vi. For HBR: the human biomedical research or health information research would reasonably be considered to contribute to the greater public good.
vii. Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

Examples when waiver or alteration of informed consent process may be appropriate:

i. Subject not fully informed about the purpose of research, when deception is part of study design;
ii. Waiver of informed consent in a retrospective review of medical records (not applicable to HBR regulated under the HBRA 2015);
iii. Waiver of documentation of informed consent to prevent any potential harm resulting from a breach of confidentiality; or
iv. Some research about natural behavior may require that subjects be unaware that the research is taking place.

Waiver of Documentation of Informed Consent

The investigator way request to waive the requirement to obtain written documentation of informed consent (i.e. a signed consent form) for some or all subjects. The investigator is required to provide their justifications in the request to waive the requirement to obtain written documentation of informed consent in the ethics application (Annex E – Waiver of Informed Consent).

i. That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

ii. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or

iii. If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

B3.4 Re-consent

When is Re-consent Necessary?

When a **substantive change** has been made to the study protocol / consent such as:

i. New findings that change the risk/benefit profile including the identification of new risks, an increase in the magnitude of known or suspected risks, or a decrease in the expected benefit.
ii. Study procedures have been added, modified, or removed
iii. New alternative treatments become available.

For **research involving the participation of children**, when a minor participant reaches the age of 21 and is still undergoing research procedures / previously collected samples are still being utilized / if medical records will continue to be accessed/reviewed, re-consent is necessary, unless PIEC approves a waiver of consent for these purposes.

For research involving **adult participants with decisional impairment**, if the condition causing the participant's decisional impairment is of an intermittent or temporary nature, the informed consent process should include a mechanism for obtaining the participants' direct informed consent to participant in the research upon regaining decision making capacity.

The original consent was obtained improperly:

i. Consent was obtained by an unauthorised individual.
ii. Consent was obtained utilizing the incorrect version of the document.
iii. Consent was obtained but the investigator failed to include one of the research procedures or one of the common risks of the study intervention.

A change to consent form language is initiated by PIEC, the regulatory agency e.g HSA or FDA, the sponsor or other entity which alters the information originally provided.

Methods of Re-consent or Notification

To determine an appropriate method for re-consenting subjects, the following shall be considered:

i. the subject population,
ii. the status of the participants,
iii. the information to be conveyed and
iv. the length the consent documents.

Consent Form Addendum

- This can be used when new information needs to be communicated to already enrolled participants.
- The document consists of 3 main sections (new information, right to withdraw and voluntary consent) with the new information being the focus of the document.

Consent with a Revised Full Document

- The full consent document is revised and re-signed by enrolled subjects.

Letter / Email (for information)

- The letter should contain 3 elements of consent (new information, right to withdraw, contacts for questions)
- The nature of the new information dictates whether participants need to return an acknowledgement.
- The documentation on medical/research record should include how information was provided, by whom and the date of the interaction.

Verbal Communication (telephone call or face-to-face etc)

- The nature of the new information dictates whether a script is necessary.
- The script should contain 3 elements of consent (new information, right to withdraw, voluntary consent if applicable)
- The documentation on medical/research record should include how information was provided, by whom, the date of the interaction and whether verbal consent is given.

B4. What is the timeline for review?

B4. What is the timeline for review?

Full Board Review

- The Principal Investigator will expect to receive the outcome of review by the last working of the month when full board review meeting was conducted for the research proposal

Expedited Review / Exemption

- The Principal Investigator will expect to receive the outcome of review within 3-4 weeks from the receipt date of submission dossier.

B5. What are the outcomes of review?

B5. What are the outcomes of review?

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

Approved - The investigator is not required to change any aspect of the protocol or consent document. The approval starts from the date of review and valid for one year, unless the committee has granted a shorter period of approval.

Conditional Approval - Minor revisions required. Investigator must not commence the study until the revisions have been approved and received the final approval letter from PIEC. The approval starts from the date of final approval given until one year from the date of review, unless the committee has granted a shorter period of approval.

Deferment of Decision - This means that the magnitude or number of concerns, questions or problems is such that the committee must review a revised study application again at a convened meeting.

Not Approved - The study design is problematic or ethically unacceptable. Such determination will be made at full board review.

Suspend or Terminate Approval - There is major concern with safety on an approved research.

Requiring Full Board Review - Any study that qualifies for expedited review procedures may be escalated to full board review if deemed necessary by the Chairperson or his/her designee.

B6. Can decisions be appealed?

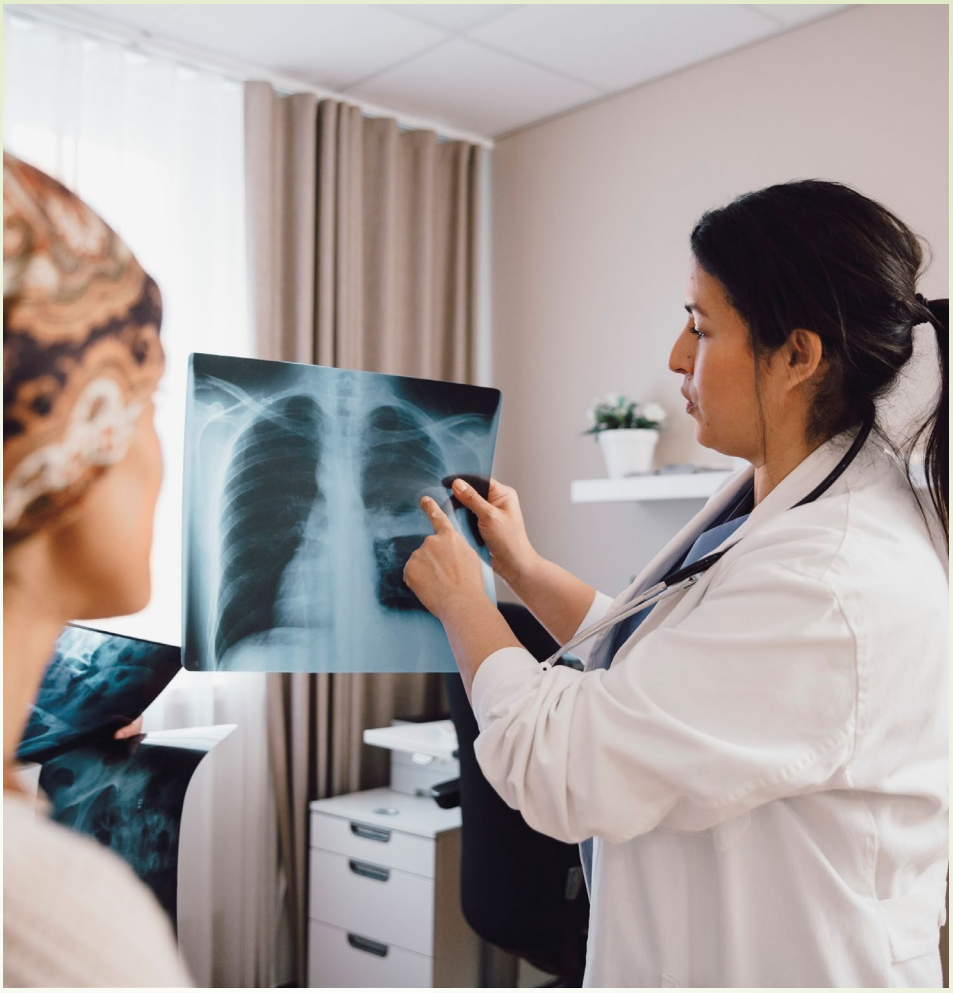
B6. Can decisions be appealed?

If the PIEC disapproves a research proposal, the reasons for the disapproval will be provided to the Principal Investigator in writing.

The Principal Investigator, within 30 days after the decision of PIEC may submit an appeal to the Chairperson. Appeal shall be in writing and contains the rationale for the appeal.

The appeal request will be considered at the next available full board meeting, provided the submission is received before the submission deadline for full board review.

C. Post-Approval Requirements



C1. What are the post-approval submissions required?

After an approval is granted for a study, the Principal Investigator shall undertake his/her due diligence to ensure that the following post-approval submission requirements are being complied with:

a. Study Amendment
b. Continuing Review
c. Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)
d. Noncompliance
e. Study Closure

C2. Study Amendment

C2. Study Amendment

No deviation from, or changes to, the protocol should be implemented without documented approval from the PIEC, except where necessary to eliminate apparent immediate hazard(s) to the study subjects, or when the change(s) involves only logistical or administrative aspects of the research (e.g. contact number etc).

Principal Investigator is responsible to submit proposed changes in a research study to PIEC for review. No changes shall be initiated before approval for the amendment is granted by PIEC.

Any deviation from, or a change to, the protocol to eliminate an immediate hazard should be promptly reported to the PIEC within seven (7) calendar days.

Submission Requirements for Study Amendment

Principal Investigator (PI) / Coordinating PI applying for Study Amendment must submit:

- Study Amendment Cover Note
- The amended document(s) with tracked changes
- The clean copy of the amended document(s)
- Any other documentation that the PIEC may specifically request

Study Amendments may include amendment to protocol, amendment to consent document or other recruitment materials, change of Principal Investigator or investigator(s) or change of recruitment target etc.

Types of Revision and Review Categories

Administrative Change	Expedited Review
Minor Revision	Expedited Review
Substantive Revision	Full Board Review

Administrative Change- Administrative changes such as change in addresses, contacts, etc, and correction of typographical and grammatical errors will be reviewed via expedited procedures. No review fee will be applied.

Minor Revision- A minor revision is one which, in the judgment of reviewer, makes no substantial alteration in

- the level of risks to participants;
- the research design or methodology;
- the number of participants enrolled in the research;
- the qualifications of the research team;
- the facilities available to support safe conduct of the research; or
- any other factor which would warrant review of the proposed changes in a convened meeting.

Addition of procedures that

- involve no more than minimal risk, and
- eligible for categories of research that can be reviewed using the expedited procedure.

Examples

Some examples of changes include, but are not limited to:

- Changing the number of research participants
- Adding co-investigators
- Minor changes to recruitment procedures, recruitment materials or submission of new recruitment materials to be used in accordance with approved recruitment methods
- Minor changes to study documents such as surveys, questionnaires or brochures
- New study documents to be distributed to or seen by subjects that are similar in substance to those previously approved
- Changes in payment to subjects or the amount subjects are paid or compensated that are not significant enough to affect the risk/benefit ratio of the study
- Decrease in the number and volume of sample collections as long as they do not negatively alter the risk/benefit ratio of the study
- Removal of an invasive procedure

Major Revision - Any change that negatively affect the risk benefit ratio or significantly affect the nature of the study and does not meet the criteria for minor revision, as set forth above, will be considered a substantive amendment.

Some examples of changes that should be reviewed at a convened meeting include, but are not limited to:

- Significant changes in study design, such as the addition of a new subject population or the elimination of a study arm
- Adding or revising eligibility criteria that add a potentially vulnerable population or have impact on the research design or clinical endpoint
- Changes in inclusion/exclusion criteria that impact the risk/benefit ratio of the study
- Adding procedures that increases the overall risk to the subjects involved in the study
- Updating the consent document to include a newly identified side effect or adverse event related to the study drug
- Changing the drug dose or route of administration
- Change in the principal investigator.
- Changes that adversely affect the risk/benefit ratio of the study or specifically increase the risk to subjects
- New risk information that is substantial or adversely affects the risk/benefit ratio of the study
- Significant changes to the study documents to be distributed to or seen by subjects
- New study documents to be distributed to or seen by subjects that include information or questions that are substantively different from materials already approved by PIEC

*For change in PI, although the first presumption is to first view this as a major modification, it may be considered minor (and thereby can be reviewed as expedited) if the following criteria are fulfilled:

The individual

- must have known research experience in the same therapeutic area and same trial phase,
- is well-qualified to carry out the research in the designated research role, and
- has not been involved in any study that was suspended / terminated by an IRB or regulatory authority due to misconduct / non-compliance.

If the criteria are not fulfilled, a change in PI must be reviewed by the full board.

C3. Continuing Review

C3. Continuing Review

Continuing review and re-approval of a research project at least annually is required so long as the project continues to involve human subjects. PIEC considers a research project to continue to involve human subjects as long as the investigators conducting the research continue to obtain:

- Data about the subjects of the research through intervention or interaction with them; or
- Identifiable private information about the subjects of the research.

When the only remaining activity of a research project involves the analysis of aggregate data sets without individual subject identifiers, no further continuing review is necessary. Refer to section on Study Closure.

Submission Requirements for Continuing Review

Requirements: Principal Investigator (PI) / Coordinating PI applying for renewal of approval of a research proposal must submit the following at least 4 weeks prior to expiry date:

- PIEC Study Status Report Form
- Any other documents as indicated in PIEC Study Status Report Form (e.g. DMC Outcome Letter, Periodic Safety Reports
- Study Amendment can be submitted at the time of continuing review.

Study Status that requires renewal of approval upon expiry:

Not Yet Initiated - No research-related activities have been performed since initial approval.

Ongoing - Research-related activities are still being performed.

Enrolment Closed, Subject Follow Up Only - The study is permanently closed to new participants, AND all participants have completed research-related interventions, AND the research remains active only for long-term follow up

Last Patient Last Visit Over, Data Analysis Ongoing – Only for single-centre study. There will be no more contact with subjects or collection of individually identifiable data and the remaining research activities are limited to data analysis.

Level of Review

Research activities that initially qualified as minimal risks and underwent initial expedited review and approval can continue as expedited review procedure during the time of continuing review, unless changes in procedures or intervention cause the activity to be more than minimal risks.

Studies that initially went through a convened meeting will continue with full board review at the time of continuing review, unless circumstances under which the use of expedited review is applicable for continuing review. Refer to next page.

Category 1

a. the research is permanently closed to the enrollment of new subjects; and
b. all subjects have completed all research-related interventions; and
c. the research remains active only for long-term follow-up of subjects;

Category 2

a. no subjects have been enrolled
b. no additional risks have been identified;

Category 3

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

Category 4

a. the committee has determined and documented at a full board meeting that the research involves no greater than minimal risk and no additional risks have been identified.

For a multi-centre study, the expedited review procedure may be used only when the criteria for expedited review is met by all PIEC governed study sites.

Continuing Review Submission Deadline

Continuing Review which require Full Board Review will follow the same submission deadline as new applications.

Continuing review that qualifies for expedited procedures may be submitted to the PIEC on any working day.

Lapse in Ethics Approval

A lapse in ethics approval of research occurs whenever an investigator has failed to provide continuing review information to PIEC or PIEC has not conducted continuing review and re-approved the research – with or without conditions – by the expiration date of ethics approval.

In such circumstances, all research activities involving human subjects, including patient accrual activities, must stop after ethics approval expired.

C4. UPIRTSO Reports (Unanticipated Problems Involving Risks to Subjects and Others)

C4. UPIRTSO Reports (Unanticipated Problems Involving Risks to Subjects and Others)

Definition

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

Unanticipated problems involving risks to Subjects or Others (UPIRTSO)
A UPIRTSO includes any incident, experience, or outcome that meets all of the following criteria:

I. Unexpected (in terms of nature, severity, or frequency) given
   a. The research procedures that are described in the protocol-related documents.
   b. The characteristics of the subject population being studied;
II. Related or possibly related to participation in the research; and
III. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

It includes other types of unanticipated problems that are not considered adverse events, i.e. unanticipated problems involving social or economic harm, instead of physical or psychological harm; for example, breach of confidentiality.

In other cases, there are unanticipated problems place subjects or others at increased risk of harm, but no harm occurs, e.g. Error in medication that did not result in any adverse event.

Reportable Events

Any incident, experience, or outcome that meets the three criteria stated above must be reported to PIEC.

Assessing Expectedness

Any unanticipated problems, including adverse events that the nature, severity, or frequency of which is not consistent with the known or foreseeable risk that are described in the protocol, informed consent document or any applicable investigator's brochure and not consistent with the expected natural progression of any underlying disease, disorder or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Assessing Causality

Any unanticipated problems, including adverse events that are determined to be at least partially caused by the procedures involved in the research are considered **related or possibly related** to participation in research.

Any unanticipated problems, including adverse events determined to be solely caused by (1) an underlying disease, disorder, or condition of the subjects; or (2) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject are considered **unrelated** to participation in the research.

The following conditions might help to assess causality:

- the event has a reasonable temporal relationship to the intervention;
- the event could not have been produced by the underlying disease states;
- the event could not have been due to other non-study interventions;
- the event follows a known pattern of response to the intervention; or
- the event disappears with cessation of intervention.

Assessing whether an unanticipated problem places subjects or others at a greater risk of harm

The third criterion is to determine whether the adverse event is serious. PIEC defines serious adverse event as any adverse event that

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgement, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above.

Other adverse events that are unexpected and related or possibly related , but not serious, will be considered a reportable UPIRTSO if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Examples of others reportable events:

a. 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 PIEC.
    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 PIEC.

b. A breach of confidentiality.

c. Change in FDA (or equivalent regulatory body) labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

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

e. Incarceration of a participant in a protocol not approved to enroll prisoners. (PIEC does not review research involving prisoner)

f. Event that requires prompt reporting to the sponsor.

g. Sponsor imposed suspension for risk.

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

i. New information that may adversely affect the safety of the participants or the conduct of the clinical trial.

j. Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.

Reporting Timeline and Requirements

Investigators must report UPIRTSOs to PIEC within seven (7) calendar days after first knowledge by the investigator.

For locally registered products, please only submit internal and external UPIRTSO events that arise from the same **clinical trial protocol that is approved by PIEC**.

For locally unregistered products (including different use from local approved label), both internal and external UPIRTSO events, including events from other clinical trial protocols using the same investigational products have to be submitted to PIEC.

A. Internal UPIRTSO

1. Internal UPIRTSO are those unanticipated problems experienced by subjects enrolled by the investigator(s) or others that occurred at the study sites conducting the research under the oversight of PIEC.
2. Investigators must report an internal UPIRTSO to PIEC **within seven (7) calendar days** after first knowledge by the investigator.
3. Events involving death of subjects, whether or not related to study participation, must be reported immediately – **within 24 hours** after first knowledge by the investigator.
4. For multi-sites study, the reporting of internal UPIRTSO is not limited to Coordinating PI. Site PI of the site where the reported problem occurred can report to PIEC directly but is also responsible to keep the Coordinating PI informed.
5. For active comparator, please submit internal UPIRTSO events that arise from the clinical trial protocol that is studied in Singapore.

B. External UPIRTSO

1. External UPIRTSO are those unanticipated problems experienced by subjects or others at other study sites engaged in the research. These include overseas sites or local sites that are not under the oversight of PIEC.
2. For multi-sites study, the Coordinating PI is responsible for reporting of external UPIRTSOs.
3. All external UPIRTSO, including unanticipated problems from other protocols using the same investigational product(s) must be reported within **seven (7) calendar days** after first knowledge by the investigator.
4. External UPIRTSO associated with active comparator used in a clinical trial or involving death that is not related to the study need not be reported to PIEC.

C5. Non-Compliance

C5. Non-Compliance

What is Non-compliance?

Any action or activity associated with the conduct or oversight of research involving human participants that fails to comply with laws or regulations, institutional policies, the requirements or determinations of ethics committee or regulatory agency or the provision of the approved research study is considered non-compliance. A protocol deviation constitutes noncompliance.

Complaints or reports of noncompliance from someone other than the Principal Investigator or study team personnel are handled as allegations of noncompliance until such time that the report is validated or found to be invalidated or dismissed.

Reporting Requirements

All **serious** or **continuing** noncompliance shall be reported to PIEC.

Non-compliance determined to be neither serious nor continuing need not be reported.

Principal Investigators are also required to report results of audits or inspections conducted by sponsors, other external entities such as the FDA, HSA or internal oversight committees.

PIEC may receive an allegation / a report of non-compliance by many means that include, but are not limited to:

- Voluntary notification by the PI
- PI not responding to PIEC's queries / reminders for renewal
- Information given by other members of the research team
- Monitoring reports
- Audit reports
- Complaints from research subjects

Serious Non-compliance

Defined as any behavior, action or omission in the conduct or oversight of human research that, in the judgment of PIEC, has been determined to:

i. adversely affect the rights and welfare of participants;
ii. result in a detrimental change to a participant's clinical or emotional condition or status;
iii. compromise the integrity or validity of the research;
iv. result from willful or knowing misconduct on the part of the investigator(s) or study staff; or
v. harm or pose an increased risk of substantive harm to a research participant.

Any wilful violation of policies, laws and regulation may also constitute serious noncompliance.

Examples of serious noncompliance may include, but are not limited to, the following:

1. Conducting research that requires direct interaction or interventions with human participants without first obtaining IRB approval;
2. Failing to submit a continuing review application to PIEC before study expiration for an ongoing study (resulting in a lapse of PIEC approval) and continuing with engaged activities;
3. Failing to obtain and/or document a participant's informed consent when study is not eligible for waiver of consent;
4. Failing to retain copies of informed consent forms (signed or unsigned);
5. Performing a study procedure not approved by PIEC; or failing to perform a required study visit or procedure that, in either case, may affect subject safety or data integrity, unless changes are implemented to avoid imminent harm to subjects;
6. Failing to follow the safety monitoring plan;
7. Enrolling study subjects after the PIEC-approval of a study has expired;
8. Failing to report serious adverse events and/or unanticipated problems to PIEC; or
9. Any other instances as determined by PIEC.

Continuing Non-compliance

Defined as a pattern of noncompliance that

i. indicates a lack of understanding or disregard for the regulations or institutional requirements that protect the rights and welfare of participants and others;
ii. suggests a likelihood that noncompliance will continue without intervention; or
iii. involves frequent instances of minor noncompliance.

Examples of continuing noncompliance may include, but are not limited to, the following:

1. Continuing to conduct research after PIEC orders a stop due to an issue of noncompliance
2. Repeated late submissions of reportable events
3. Repeated lapses of PIEC approval
4. Repeated failure to comply with a PIEC-approved protocol
5. Repeated informed consent discrepancies

Protocol Deviation

Defined as any alteration/modification to a PIEC-approved protocol made without prior PIEC approval.

A protocol deviation constitutes noncompliance.

Whether a protocol deviation qualifies as minor or serious noncompliance depends upon whether, under the specific circumstances, it may

i. adversely affect the rights and welfare of participants;
ii. harm or pose an increased risk of substantive harm to a research participant;
iii. have a substantive effect on the scientific value of the data collected; or
iv. result from willful or knowing misconduct on the part of the investigator(s) or study staff.

Examples of serious protocol deviation may include, but are not limited to, the following:

1. Enrolling participants who fail to meet the eligibility criteria in a protocol;
2. Failing to withdraw a participant who develop withdrawal criteria;
3. Medication error / subject received the wrong treatment or incorrect dose;
4. Subject received a prohibited concomitant medication;
5. ECG not performed at a scheduled visit in a study where the primary endpoint is based on the ECG findings;
6. Missed PK sampling for early phase trials.

Submission Timeline and Requirements

Principal Investigator, members of the research team or other individuals who believe that an instance of serious or continuing noncompliance has occurred must report it to PIEC **within seven (7) calendar days** of becoming aware of the noncompliance, using the PIEC Noncompliance Report Form.

Principal Investigator (PI) / Coordinating PI reporting protocol deviation must submit the following document(s) to PIEC:

- PIEC Noncompliance Report Form
- Other relevant documents (if applicable)

C6. Study Closure

C6. Study Closure

Study Completion

When a study is completed, the PI should submit study completion reports within thirty (30) calendar days after completion of the study. Completion reports should be submitted using the PIEC Study Status Report Form.

The study is considered closed should the research activities no longer involve human participants. A research project no longer involves human subjects once the investigators have finished obtaining data through interaction or intervention with subjects or obtaining identifiable private information about the subjects, which includes the using, studying, or analyzing identifiable private information.

Study Suspension / Termination by Institution, PI or Sponsor

When a study is suspended or terminated by the Institution, PI or the sponsor, the PI should promptly inform PIEC about that change in status and provide the reason(s) for the termination or suspension using the PIEC Study Status Report Form, within seven (7) calendar days.

In the event that study activities are ongoing for enrolled subject at the time the decision of study termination is determined, the PI shall maintain a valid ethics approval until all subjects have completed all required safety follow-ups as stipulated in the approved protocol and ensure that all subjects safely exit from the study.

For suspended study, the PI shall indicate the period of suspension, if the information is available.

Study Withdrawal

A study is considered withdrawn when the study is stopped before site initiation. The PI should promptly inform PIEC about that change in status and provide the reason(s) for the withdrawal using the PIEC Study Status Report Form, within seven (7) calendar days.

Expired Study

If a Principal Investigator has failed to provide continuing review material to PIEC or PIEC has not re-approved a research study by the specified approval expiry date, the study approval expires.

The research activity must stop, unless a convened PIEC meeting decides that the study may go on in order to protect welfare and safety of subjects.

No research activities, including screening, enrollment, interventions, and interactions, and collection of identifiable data can occur on expiration date or after, unless specific permission is granted by PIEC.

Study Suspension / Termination by PIEC

The PIEC may suspend or terminate a study that is not being conducted in accordance with regulatory requirements / PIEC requirements or that has been associated with unexpected serious harm to the research subjects.

Some examples of situations when a PIEC may suspend / terminate a research study include, but are not limited to:

i. Inappropriate involvement of human subjects in research;
ii. Inhibition of the rights or welfare of participants;
iii. Serious or continuing noncompliance with regulations or PIEC procedures;
iv. New information regarding increased risk to human participants; or
v. Expiry of approval.

Investigators receiving repetitive suspensions or terminations may necessitate PIEC actions for serious and continuing noncompliance.

Reactivation following Suspension

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

i. Duration of suspension;
ii. Circumstances surrounding suspension;
iii. Enrollment status of the study;
iv. Level of risk involved in the study; and
v. Any other issue deemed significant by the PIEC.

Submission Requirements for Study Closure

Notification on Study Closure shall include the following documents

1. PIEC Study Status Report Form, with study status stated clearly as:
    i. Completed - No more research-related activities at site, including contact with subject, collection of individually identifiable data or data analysis.
    ** For multi-centre study involving local and/or overseas sites, the study may be considered 'completed' when access to individually identifiable data is no longer required at sites under the oversight of PIEC.*
    ii. Withdrawn - The study is stopped before site initiation.
    iii. Terminated - The study is stopped after site initiation.
    iv. Suspended – The study is temporarily stopped.

2. Any other documents as indicated in PIEC Study Status Report Form

3. Summary of study outcome and/or with the final study report
    - only applicable for completed study
    - *to be submitted not more than 3 months after study completion. Completion of the study, in this instance, is when the last study site in a global study or the last study site in a local study is no longer involved in any research activities.*

END