Parkway Independent Ethics Committee (PIEC)

Investigator Manual

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Contact Information

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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 6349 5747.

Yours faithfully,
PIEC Secretariat
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A. Before Study Start-up
A1. What is considered research?

- A1.1 Defining Research
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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.

**The definition of human biomedical research under Bioethics Advisory Committee Guidelines for IRBs**

Human 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.

One or more of the following conditions will apply to any proposed human biomedical research:

i. The research involves intervention with respect to, interaction with, or observation of one or more human participants;

ii. The research will use of manipulate human biological materials (e.g. human cells, tissues, organs and body fluids);

iii. The research entails the systematic review, analysis, use or publication of previously compiled identifiable (identified or reversibly de-identified) medical or personal information or biodata;

iv. The research topic is sufficiently sensitive to likely raise questions of public acceptability or public policy (e.g. research on human embryos or human–animal combinations – MOH approval is required); or

   - The research could be considered sensitive by virtue of the nature of the personal information it proposes to gather.
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.

Medicinal Purpose

- Any one or more of the following purposes:
  - treating or preventing disease;
  - diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;
  - contraception;
  - inducing anaesthesia;
  - otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way.

Subject

- A person to whom the test material is to be administered in a Clinical Trial.
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. Personal Data Protection Act
10. DHHS Regulations 45 CFR 46 – applicable for all research funded by US Federal Funds e.g. funded by NIH, NCI, NIAIDS etc.
11. 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**

- An 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.

**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.
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.

**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, 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 and collaborators must fulfil one of the following training requirements as they have the responsibility to conduct the research in compliance with Good Clinical Practice (GCP).

1. Good Clinical Practice (GCP) Course: This course can be conducted in classroom/lecture format by a renowned local institution/organization. Alternatively a participant can learn this course through a web-based learning platform established by a reputable organization e.g. Collaborative Institutional Training Initiative (CITI). Certificate of completion is required for submission to PIEC. This is compulsory for all clinical trials.

2. Human Subject Research (HSR) Course by Collaborative Institutional Training Initiative (CITI): CITI Program’s HSR series consists of modules from two basic tracks, Biomedical (Biomed) and Social–Behavioral–Educational (SBE), and a set of Additional Modules of Interest.

3. GCP course conducted by pharmaceutical companies: The materials used shall be submitted to PIEC for review and approval. Training certificates and proof of attendance shall be included in the submission to PIEC.
A5. What are the responsibilities of a PI/Investigator?

- A5.1 Declaration of Conflict of Interest to PIEC
A5. What are the responsibilities of a PI / 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

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<th>Conflicting Interest</th>
<th>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.</th>
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<td>Financial Interest</td>
<td>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.</td>
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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 (e.g. subject’s welfare, integrity of research) may be biased by a secondary interest (e.g. 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
All new applications have to be made in hard copy and soft copy to:

Parkway Independent Ethics Committee
Haw Par Centre
180 Clemenceau Avenue, #06–01, Singapore 239922
Email: piec@parkwaypantai.com

For full–board review, the submission dossier should consist of the following:
- 1 original hard copy
- 11 duplicate hard copies
- Soft copy (to be sent by email)

For expedited review and all other notifications, the submission dossier should consist of the following:
- 1 original hard copy
- Soft copy (to be sent by email)

Each dossier should be organized in a 2–holes file with separators.

Applicants may obtain the latest forms and information on submission deadlines and review fees on our website https://www.parkwaypantai.com under the page ‘For Medical Professionals’ 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.

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

Review Fees:
Cheque payment should be crossed and made payable to “Parkway Hospitals Singapore Pte Ltd”.

*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);
• uncanulated 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 – Normal Educational Practices and Settings**
Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:

- Research on regular and special education instructional strategies; or
- 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:
  - Evaluation of a radically new instructional strategy
  - Use of random assignment of subjects to different instructional methods
  - Educational research involves deception or withholding of information from subjects
  - Physical education involves intense exercise

**Exemption Category 2 – Anonymous Educational Tests, Surveys, Interviews, or Observations**
Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observations of public behavior, unless:

- Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
- Any disclosure of the human subjects’ responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Examples of research that are not exempt under this category:

- 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.
- 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.
Exemption Category 3 – Identifiable Subjects in Special Circumstances
Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under Exemption Category 2, if:
• The human subjects are elected or appointed public officials or candidates for public office; or
• Singapore’s legislation/ federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Exemption Category 4 – Collection of Existing Data
Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Examples of research that are not exempt under this category:
• Existence of identifier, such as a code that can be used to identify a subject, even though the investigators do not have access to the subject’s identity which is linked to the data or specimen.
• Research 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 – Public Benefit or Service Programs
Research and demonstration projects which are conducted by or subject to the approval of government agencies, and which are designed to study, evaluate, or otherwise examine:
• Public benefit or service programs;
• Procedures for obtaining benefits or services under those programs;
• Possible changes in or alternatives to those programs or procedures; or
• Possible changes in methods or levels of payment for benefits or services under those programs.
**Exemption Category 6 – Taste and Food Evaluation and Acceptance Studies**

Taste and food quality evaluation and consumer acceptance studies; If wholesome foods without additives are consumed; or 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 Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture or any local government agencies or statutory boards. 

Examples of research that are not exempt under this category: Consumption of any type or volume of food that has any potential risks such as indigestion or vitamin deficiencies. Consumption of alcohol, vitamin, or supplements such as protein powder, creatine, glucosamine chondroitin sulfate etc.

**Exemption Category 7 – Non–Human Research**

Research activities involve only Commercial Cell Lines; Unidentifiable human pathological specimens; Bacteria/Virus isolates with no direct human subject contact or identifiers.

**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)
   • 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 non-Parkway 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)
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 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 E–Waiver of Informed Consent, if applicable  
VI. 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.
Basic Elements of Informed Consent Documents (1 of 3)

1. The clinical study involves research or the investigational nature of the research.

2. The purpose of the research and why subject is invited to participate.

3. The expected duration of the subject’s participation in the research.

4. The approximate number of subjects involved in the research from study site, Singapore and global.

5. Subjects are informed about any financial incentives being provided to the researcher or the institution from the sponsor or a grant.

6. Subjects are explicitly informed of any and all potential conflict of interests of the research team.

7. The treatment(s) or intervention(s) to be administered in the research and the probability for random assignment to each treatment.

8. The procedures to be followed in the research, including all invasive procedures.

9. The responsibilities of the subject.

10. Those aspects of the research that are experimental.

11. A description of any reasonably foreseeable risks, discomforts or inconveniences to the subject or to an embryo or fetus, if the subject is or may become pregnant or to a nursing infant.

12. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
Basic Elements of Informed Consent Documents (2 of 3)

13. The alternative procedures or of treatments that may be available to the subject, and the potential benefits and risks of such alternatives.

14. For research involving more than minimal risk, whether compensation and/or medical treatment is available to the subject in the event of injury arising from participation in the research.

15. The anticipated prorated payment (i.e. the amount and schedule), if any, to the subject for participating in the research as reimbursement / compensation for transport and time.

16. Any anticipated expenses the subject is likely to incur as a consequence of participating in the research.

17. Assurance that subject’s participation in the research is voluntary and that the subject may refuse to participate or withdraw from the research, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

18. A statement that significant new findings becomes available that may be relevant to the subject’s willingness to continue participation in the research will be informed to the subject or subject’s legally acceptable representative in a timely manner.

19. The foreseeable circumstances and/or reasons under which the subject’s participation in the research may be terminated without regard to the participant’s consent.
Basic Elements of Informed Consent Documents (3 of 3)

20. The monitor(s), the auditor(s), the health authority 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 and that, by signing a written informed consent form, the subject or the subject’s legally acceptable representative is authorising such access and the possibility that the licensing authority may inspect the records.

21. 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. If the results of the trial are published, the subject’s identity will remain confidential.

22. The person(s) to contact for further information regarding the research or research-related injury.

23. The person(s) to contact and contact details for further information regarding the rights of subjects

24. Any other information that PIEC may require to be given.
Additional Elements of Informed Consent, as appropriate (1 of 2)

1. When the research involves tests such as HIV testing, that require mandatory reporting to the Ministry of Health, if result is positive.

2. 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.

3. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

4. Whether individually-identifiable information obtained from the subject will be used for future biomedical research.

5. Where applicable, whether biological material taken from the research subject will be destroyed, discarded or stored for future research.

6. Whether the participation of the subject involves information in individually-identifiable form.

7. Circumstances where subject will be contacted for further consent, for example:
   i. Changes in proposed research;
   ii. Serious adverse event that will lead to a change in the proposed research; or
   iii. The development of capacity by minor to make decisions.

8. Whether the research subject would wish to be re-identified in the case of an incidental finding if the proposed research expressly provides for such re-identification.
Additional Elements of Informed Consent, as appropriate (2 of 2)

9. Subject’s right to withdraw his or her consent and the limitations of such withdrawal:

   i. When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remain part of the study database and may not be removed.

   ii. A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant must distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of confidentiality of the participant's information.

   iii. If a participant withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information, the researcher must obtain the participant's consent for this limited participation in the study (if such a situation was not described in the original consent document).

   iv. If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.
Required Elements of Informed Consent – Removal, donation or use of human tissue (1 of 2)

1. The specific research purpose for which the tissue is intended to be used; if not available, the purpose may be stated as for general research.

2. 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.

3. For research involving persons who are unable to give consent – The proposed areas of research approved by the ethics committee in a case where it has waived the requirement that the removal of the tissue is primarily for a therapeutic or diagnostic purpose.

4. The reasonably foreseeable risks, discomforts or inconveniences to a living donor arising from the removal of the tissue.

5. 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 derived from the use of the tissue.

6. The donor’s right to withdraw his or her consent and the limitations of such withdrawal.

7. Any compensation and treatment available to the donor in the event of injury arising from participation in the process of tissue donation.

8. Any anticipated expenses the donor is likely to incur as a consequence of donating tissue.

9. The extent to which records identifying the donor will be kept confidential.
Required Elements of Informed Consent – Removal, donation or use of human tissue (2 of 2)

10. Whether individually-identifiable information obtained from the tissue donor will be used for future research.

11. Where applicable, whether biological material taken from the tissue donor will be destroyed, discarded or stored and used for future research.

12. The circumstances under which the donor will be contacted for further consent.

13. Whether the tissue donation would result in the use of the donor’s tissue in an individually-identifiable form.

14. Whether the tissue will be used in restricted human biomedical research involving human–animal combinations.

15. Whether the donor would wish to be re-identified in the case of an incidental finding if the future research expressly provides for such re-identification.

16. The person to contact to obtain further information on the purposes for which tissue will be used and to provide feedback in relation to such purposes.

17. Whether the tissue will be exported or removed from Singapore to a place outside Singapore.
**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.

The Investigator is required to provide justifications/evidence that:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
5. The research is not subject to FDA regulations.

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

1. Subject not fully informed about the purpose of research, when deception is part of study design;
2. Waiver of informed consent in a retrospective review of medical records;
3. Waiver of documentation of informed consent to prevent any potential harm resulting from a breach of confidentiality; or
4. 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 may request to waive the requirement to obtain written documentation of informed consent (i.e. a signed consent form) for some or all subjects if one of the following applies:

- i. That the only record linking the subject and the research would be the consent document;
- ii. The principal risk would be potential harm resulting from a breach of confidentiality;
- iii. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; and
- iv. The research is not subject to FDA regulations

OR

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

The investigator is required to provide their justifications in the request to waive the requirement to obtain written documentation of informed consent.
B3.4 Re-consent

When is Re-consent Necessary?

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 participate in the research upon regaining decision making capacity.

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.

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.

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.
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 2 weeks from the receipt date of submission dossier.
- The receipt date refers to the date when printed copies are received and acknowledged by PIEC Secretariat. Soft copies can be forwarded via email to piec@parkwaypantai.com.
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?
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 (UIRTSO)
d. Noncompliance
e. Study Closure
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**

<table>
<thead>
<tr>
<th>Administrative Change</th>
<th>Expedited Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Revision</td>
<td>Expedited Review</td>
</tr>
<tr>
<td>Substantive Revision</td>
<td>Full Board Review</td>
</tr>
</tbody>
</table>

**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)
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(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.

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.

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

**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

**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.