Parkway Independent Ethics Committee
Policies and Procedures Manual

Section A: Introduction

1.1 Purpose and Scope of the Manual

This manual contains a compilation of PIEC's PnPs in relation to the review of Human Biomedical Research and a list of the PIEC's PnPs to be adopted all Research Institutions appointing PIEC as the reviewing IRB under Human Biomedical Research Act 2015.

1.2 Applicability

The policies and procedures set forth in this manual are applicable to the Research Institution that appoints PIEC for the compliance of Key Focal Area: RI-IRB Operations. It is the responsibility of the Research Institution to state in its own PnP/Work Instruction or other written documentation for choosing to adopt PIEC's PnPs in relation to the review of its HBR for the purpose of transparency and clarity.

Note: Researchers shall refer to the Investigator's Manual for PIEC submission and reporting requirements.

1.3 Revision and Maintenance of the Manual

The manual will be maintained by PIEC Secretariat. Any revisions will be notified to the Principal Person In Charge (PPIC) of the Research Institution.

Section B: List of Policies and Procedures

The list of Policies and Procedures included for the purpose of this manual:

Contents

Section C: Policies and Procedures

1 Administration and Functions of Parkway Independent Ethics Committee

1.1 Role

1.1.1 The role of Parkway Independent Ethics Committee (PIEC) is to protect the rights, safety, and well-being of human subjects involved in research study.

1.1.2 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 facilities of Parkway Singapore, all institutions under its oversight and non-Parkway institutions that appoints it.

1.1.3 PIEC acts on behalf of the institution that appoints it, and exercises, on its behalf, the authority and powers of that institution in matters within the terms of reference of the PIEC. As PIEC plays an integral role in the ethical governance of research, the committee reports directly to the highest level of management of its appointing institution.

1.2 Scope of Authority

1.2.1 PIEC has the authority to approve or disapprove, require modifications in, or place restrictions on all human subject research (to secure approval) in order to comply with good clinical practice, written procedures and all applicable laws and regulations.

1.2.2 PIEC has the authority to conduct continuing reviews consistent with written procedures and verify no material changes occurred since previous review.

1.2.3 PIEC has the authority to suspend or terminate approval of research that is not being conducted in accordance with PIEC requirements or that has been associated with unexpected serious harm to subjects.

1.2.4 PIEC (or its authorized representatives) has the authority to conduct the following:

a. Examine and inspect the facilities used for the conduct of the studies.
b. Observe, or have a third party observe, the consent process and conduct of research and interview subjects.
c. Audit of the research and all documents related to the studies, including research records, informed consent documents, and other study-specific data.

1.2.5 PIEC has the authority to make all above decisions independent of PHSPL, appointing institutions, other committees, other IRBs, the researchers, and the regulatory agencies.

1.3 Responsibilities

1.3.1 To safeguard the rights, safety, and well-being of all research subjects. Special attention should be paid to research that may include vulnerable subjects.

a. To assess whether the participation by the minors who lack sufficient understanding and intelligence to give consent or the class of such minors, or the adults or minors who lack mental capacity or the class of such adults or minors, if any, in the proposed research is scientifically necessary and ethically appropriate for the conduct of the proposed research.

b. When a non-therapeutic research is to be carried out with the consent of the subject's legally acceptable representative, PIEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such research.

c. Where the protocol indicates that prior consent of the research subject or the subject's legally acceptable representative is not possible, PIEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such research (i.e., in emergency situations).

1.3.2 To carry out initial review of any proposed human research on ethical grounds.

1.3.3 To assess whether the research proposals have scientific merit, as it would be unethical to subject human participants to any risk or research that is so poorly designed that it could not yield generalizable knowledge. PIEC is not expected to undertake such scientific review.

1.3.4 To review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the research subjects. Payments to a subject should be prorated and not wholly contingent on completion of the research by the subject.

1.3.5 To carry out a continuing review of the research projects approved by PIEC, on ethical grounds, through requiring submissions of annual or more regular progress reports from researchers. Except for research that is exempted, all human subject research is subject to continuing oversight and review by PIEC at least annually.

1.3.6 To evaluate the provisions for the consent process to ensure that valid consent that is appropriate to the proposed research is obtained.

a) PIEC may request more information than is outlined in general requirements for informed consent, as set forth in applicable regulatory requirements, be given to subjects when, in the judgement of PIEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

b) To assess whether the minors or the class of minors, if any, who are research subjects in the proposed research are capable of giving consent to the proposed research, having regard to the ages, psychological states and maturity of the minors or class of minors involved.
c) To assess whether there are adequate provisions for taking the consent of the minors or the class of minors, if any, who are research subjects in the proposed research.
d) To ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to research subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

1.3.7 To assess the suitability and qualifications of the researcher for the proposed research.

1.3.8 To assess the suitability of the premises for the proposed research.

1.3.9 To assess the suitability and adequacy of the system of oversight of the research institution conducting the particular research proposal.

1.3.10 To assess if the data and safety monitoring plan is adequate and if a data and safety monitoring board is necessary for the purposes of the proposed research.

1.3.11 To document its views in writing, clearly identifying the research, the documents reviewed and the dates for the following:
a) To grant its approval for the research to be conducted or continued, as the case may be;
b) To require modifications to be made to the research proposal before granting its approval or allowing the proposed research to continue, as the case may be; or
c) To disallow the conduct or continuation of the proposed research, as the case may be, with written justifications.

1.3.12 To ensure that reviews shall be conducted in confidence and maintain confidentiality of all research information such as meeting deliberations, applications, information on research subjects and any related matters.

1.3.13 To refrain from participating in the deliberation and voting of any proposed research when there is conflict of interest.

1.3.14 To ensure prompt reporting of incidents to relevant oversight entity e.g. institutional officials, funding agency, local or overseas regulatory agencies, research institutions or other Institutional Review Boards (IRBs) of any unusual or unexpected events arising from the research:
a) Internal Unanticipated problems involving risks to subjects or others (UPIRTSO) that results in suspension or termination of the study by PIEC;
b) Any serious or continuing noncompliance occurred at study sites that is given unfavourable opinion by PIEC at a convened meeting; and
c) Any suspension or termination of ethics approval.

1.3.15 To provide feedback to and maintain dialogue about applicable standards with researchers.

1.4 Term of Service

1.4.1 All members are appointed to serve on the committee, collectively, for the same term of two (2) years.

1.5 Membership

1.5.1 The PIEC must consist of at least five (5) members (i.e. voting members positions) with varying backgrounds to promote complete and adequate review of research proposals, which includes:

a) At least one (1) external lay person
b) At least one (1) external scientific person

1.5.2 Every member must be 21 years of age or older and must be a citizen or a permanent resident of Singapore; or an individual who is and has been ordinarily resident in Singapore for an aggregate period of not less than 5 years out of the 10 years preceding the date of his or her appointment or reappointment.

1.5.3 A person is disqualified from acting as a member if:

a) that person is an undischarged bankrupt;
b) that person has been convicted in Singapore or elsewhere of any offence involving fraud, dishonesty or moral turpitude;
c) that person has been convicted of an offence under the Act or the regulations; or
d) for medical reasons, that person is unable to perform his or her duties as a member, as assessed by a medical practitioner.

1.5.4 Chairperson and Vice Chairperson must be medical practitioners.

1.5.5 A person who is a member concurrently of 2 or more institutional review boards which are reviewing proposals for human biomedical research that are part of the same research or are otherwise connected or related:

a) Is not disqualified from participating in the proceedings of the boards on the ground of conflicts of interests by reason only of such concurrent memberships;
b) Must disclose his or her participation in each board's proceedings to all the other boards.

1.6 Appointment of PIEC by Research Institution under HBRA

1.6.1 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.

1.6.2 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.

1.6.3 Each PIEC member shall acknowledge receipt of appointment by RI as documentary record of his/her acceptance of the appointment and the accompanying terms of reference (TORs).

1.6.4 The PIEC Administrator shall ensure that the appointing RI receives the following documentations:

a. PIEC membership roster
b. PIEC members' declaration form
c. PIEC members' acknowledgement of receipt - Appointment of PIEC as reviewing IRB by RI

1.7 Liability Coverage

1.7.1 Members shall be formally assured that the appointing Research Institutions will provide legal protection and indemnity against liabilities that may arise in the course of the conduct of their duties carried out in good faith. Such assurance shall be stated in their appointment letters or any form of formal correspondence.

2 Determination of Human Biomedical Research

2.1 Determination of HBR Status

2.1.1 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).

2.1.2 **Restricted** human biomedical research can only be carried out by a Research Institute with MOH and IRB approval:

1. Human biomedical research involving human eggs or human embryos.
2. Human biomedical research involving
    a. the following types of human-animal combination embryos:
        i. cytoplasmic hybrid embryos;
        ii. human-animal combination embryos created by the incorporation of human stem cells (including induced pluripotent stem cells);
        iii. human-animal combination embryos created in-vitro by using
            1) human gametes and animal gametes; or
            2) one human pronucleus and one animal pronucleus;

    b. the introduction of human stem cells (including induced pluripotent stem cells) into a prenatal animal foetus or animal embryo;
    c. the introduction of human pluripotent stem cells (including induced pluripotent stem cells) into a living postnatal animal but excludes the introduction of such human pluripotent stem cells into immunodeficient mice solely for the analysis of teratoma induction;
    d. the introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into the brain of a living postnatal animal; or
    e. any entity created as a result of any process referred to in sub-paragraphs (b), (c) and (d).

2.1.3 **Prohibited** human biomedical research that cannot be conducted in Singapore:

1. Human biomedical research involving the development of human-animal combination embryos referred to in paragraph 2(a)(i) or (iii) of 3.5.5 beyond 14 days or the appearance of the primitive streak, whichever is the earlier.
2. Human biomedical research involving the implantation –
    a. of a human-animal combination embryo mentioned in paragraph 2(a)(i) or (iii) of 3.5.5 into the uterus of an animal; or
    b. of a human-animal combination embryo into the uterus of a human.
3. Human biomedical research involving the introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into the brain of living great apes whether prenatal or postnatal.
4. Human biomedical research involving the breeding of animals which have had any kind of human pluripotent stem cells (including induced pluripotent stem cells) introduced into them.

2.1.4 The researcher may be asked to propose the HBR status in PIEC prescribed form. However PIEC will make the final determination of Human Biomedical Research (HBR) status.

2.1.5 PIEC will notify the researcher of the Human Biomedical Research (HBR) Status of each proposed research in writing.

3 Conflict of Interest

3.1 Defining Conflict of Interest

3.1.1 Conflict of interest, can be defined as any situation or relationship that biases or has the potential to bias the conduct or outcome of PIEC review.

3.1.2 Conflict of interest may exist in the form of financial, non-financial, professional, business or personal interest.

3.1.3 A member is considered to have a conflict of interest if he/she or a member of their immediate family meets any of the following criteria:

i. Is involved in the design, conduct, or reporting of the research. (e.g. is a member of the research team as principal investigator, co-investigator or collaborator);
ii. Has a financial interest (salary or payments for services) in the research project (e.g. consulting fees or honoraria);
iii. Has received or will receive financial compensation with value that may be affected by the outcome of the study;
iv. Has a proprietary interest in the research, such as patent, trademark, copyright, or licensing agreement;
v. Is an Executive or Director of the agency or company sponsoring the research;
vi. Owns equity (e.g. Stocks, stock options or other ownership interests) in the agency or company sponsoring the research;
vii. Is the faculty advisor to a student seeking PIEC approval;
viii. Has an interest that may conflict with the ability to objectively review a protocol e.g. when a research proposal is submitted by the member's colleagues, be they peers, subordinates or superiors.

3.1.4 Immediate family is considered to be close relatives by birth or marriage including spouse, siblings, parents, children, in-laws, grandparents and any other financial dependents.

3.2 Identifying Conflict of Interest

3.2.1 The members are required to declare any conflict of interest, upon receipt of a research proposal for review. This is applicable for both reviews using expedited procedure and convened meeting.

3.2.2 At the beginning of each convened meeting, members are required to declare all conflict of interest or potential conflicts of interest in relation to a matter under consideration by the board at that meeting. The nature and extent of such conflicts of interest shall be recorded in the meeting minutes.

3.3 Managing Conflict of Interest

3.3.1 A member with conflict of interest may be asked to leave the meeting room during deliberation and determination of actions to be taken for the research proposal which conflict of interest exists. However they may be asked to provide information at the request of PIEC.

3.3.2 A member with conflict of interest in a research proposal does not contribute to the quorum and does not have voting rights for that research proposal which conflict of interest exists. He/she shall be excluded from the total vote available for the research proposal.

3.3.3 The name of the member and reasons for recusing from deliberation and voting shall be documented in the meeting minutes.

4 Exemption from Review

4.1 Determination of Exempt Research

4.1.1 It is the responsibility of the researcher to apply for exemption.

4.1.2 Complete application shall be forwarded to Chairperson or his/her designee(s) for review.

4.1.3 If the Chairperson or his/her designee(s) agrees and approves that the application qualifies for exemption, a formal letter of exemption shall be issued to the applicant, by indicating the specific category of exemption and any recommendation for additional protections for participants, if deemed necessary by the Chairperson.

4.1.4 For the avoidance of doubts, the determination must be made prior to initiation of research or of the activity; it cannot be made retroactively.

4.1.5 To exempt a research from review, Chairperson or his/her designee(s) is satisfied that:

i. The research involves less than minimal risk to subjects.
ii. If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
iii. Research is not an FDA-regulated research
iv. Research is not a restricted or prohibited human biomedical research
v. The study falls under one of the exemption categories listed in 3.2.

4.1.6 Once the determination has been made that a project is exempt, no continuing review of the study by PIEC is required.

4.1.7 However, if an investigator decides to modify an exempt human subjects research project in such a way that it would no longer qualify for exemption, the investigator must submit the modified research protocol to the PIEC for review prior to implementation of the modified research project

4.2 Categories of Exemption

4.2.1 **Exemption Category 1 – Research in Established or Commonly Accepted Educational Settings**
Not applicable for HBR.

4.2.2 **Exemption Category 2 – Educational Tests, Surveys, Interviews, Observations of Public Behavior**
Not applicable for HBR.

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

Not applicable for HBR.

4.2.4 **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:

1) *Applicant is required to apply for waiver of requirements for appropriate consent. Research is not exempt if waiver is not granted by PIEC.*
2) *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.*
3) *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.*

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

Not applicable for HBR.

4.2.6 **Exemption Category 6 – Taste and Food Quality Evaluation and Consumer Acceptance Studies**

Not applicable for HBR.

4.2.7 **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.*

4.2.8 **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 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:

1) *Applicant must provide documentary proof that consent to permit future research use of individually- identifiable information has been obtained.*
2) *Appropriate consent is obtained for using human tissue in research.*

4.2.9 **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.

Note: Restricted Human Biomedical Research is subject to full board review.

4.3 Possible Outcomes of Review

4.3.1 PIEC may grant approval to the exemption application if all criteria for exemption are met and the study falls under one of the exemption categories.

4.3.2 If PIEC determined that the study does not qualify for exemption, the researcher will be required to resubmit under expedited review or full board review, whichever applicable.

4.4 Notification to the Committee

4.4.1 When exemption requests are approved by the Chairperson or his/her designees(s), all the members of the PIEC will be informed of the study and review outcome at the full board meeting.

4.4.2 A monthly list of submissions that have been approved or reviewed under the exemption review procedure will be provided to all committee members for perusal.

4.4.3 All members have the opportunity to review the list and ask questions in order to ensure that the members are kept informed of the activities of PIEC outside of full board deliberations.

5 Expedited Review of Research

5.1 Determination of Expedited Review

5.1.1 PIEC Chairperson or his/her designee(s) (only members who are experienced) may conduct review under the expedited review procedure.

5.1.2 PIEC shall determine whether the submission fits the criteria for expedited review.

5.1.3 If PIEC specifically request for full board review, the research proposal will be included in the agenda of the next full board meeting.

5.2 Criteria for expedited review – Initial Review

5.2.1 To be eligible for review by expedited review procedure, a research proposal must meet all the following criteria:

i. The research activities presents no more than minimal risk to research subjects;
ii. Identification of subjects and / or their responses would 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;
iii. The research is not classified;
iv. The research is not a restricted human biomedical research and
v. The research activity is listed in 5.3 Categories of Research – Initial Review. The categories in this list apply regardless of the age of subjects, except as noted.

5.3 Categories of Research – Initial Review

5.3.1 Category 1 – Clinical Studies of medicinal / therapeutic product or medical devices only when one of the following conditions is met:

i. Research on drugs for which an investigational new drug application is not required (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
ii. Research on a medical device for which (a) an investigational device exemption application is not required; or (b) the medical device is cleared / approved for marketing and used in accordance with its cleared / approved labeling.
iii. Research on medicinal products or therapeutic products for which a Clinical Trial Certificate or Clinical Trial Authorization is not required.

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

i. 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

ii. 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.

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

Examples:

a. Hair and nail clippings in a non-disfiguring manner;
b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
c. Permanent teeth if routine patient care indicates a need for extraction;
d. Excreta and external secretions (including sweat);
e. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
f. Placenta removed at delivery;
g. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
h. Supra- and sub-gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
j. Sputum collected after saline mist nebulization.

5.3.4 Category 4 - Collection of data through noninvasive procedures routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.

- The noninvasive procedure must not involve general anesthesia or sedation routinely employed in clinical practice or 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 of nonivasive procedures:

a. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
b. Weighing or testing sensory acuity;
c. Magnetic resonance imaging;
d. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
e. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5.3.5 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 for medical treatment or diagnosis).

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

5.3.7 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.

5.4 Category 8 – Continuing Review

5.4.1 Continuing review of research previously approved by expedited review procedure:

i. no concerning issues have arisen since the last approval; and
ii. research appears to continue to satisfy all criteria for approval

5.4.2 Continuing review of research previously approved by full board meeting:

i. where all of the following are met:
   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; or

ii. where no subjects have been enrolled and no additional risks have been identified; or

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

5.5 Category 9 - Continuing Review of research not conducted under IND application or IDE, where categories 2 through 8 do not apply

5.5.1 Continuing review of research not conducted under IND application or IDE, and where categories 2 through 8 do not apply, 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.

5.6 Review of Modifications stipulated by PIEC

5.6.1 When the PIEC requests the Principal Investigator for clarifications or modifications, the Principal Investigator's reply may be reviewed and approved by expedited review.

5.7 Review of Modifications to Previously Approved Research

5.7.1 Modifications to Previously Approved research involves only minor or administrative change is eligible for expedited review procedure.

5.8 Possible Review Outcomes

5.8.1 Under expedited review procedure, the Chairperson or his/her designee(s) shall make one of the decisions listed below:

Approved – The investigator is not required to change any aspect of the protocol or consent document.

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.

Requiring Full Board Review – Any study that qualifies for expedited review procedures may be escalated to full board review if deemed necessary by PIEC

5.9 Notification to the Committee

5.9.1 When a submission is approved by the Chairperson or his/her designee(s) under expedited review procedure, all the members of the PIEC will be informed of the study and review outcome at the full board meeting.

5.9.2 A monthly list of submissions that have been approved or reviewed under the expedited review procedure will be provided to all committee members for perusal.

5.9.3 All members have the opportunity to review the list and ask questions in order to ensure that the members are kept informed of the activities of PIEC outside of full board deliberations.

6 Full Board Review of Research

6.1 Organisation of the full board meeting

6.1.1 The PIEC meetings shall be held monthly, at such other times as may be agreed by members of the PIEC, or when considered necessary by the Chairman or person acting in his absence. The PIEC shall meet to discharge its responsibilities and be free to adjourn or otherwise regulate its meetings as it deems fit.

6.1.2 A quorum is present when a majority (i.e. more than half) of the committee members are present, but no less than five (5) members, and must, at minimum, include the following:

i. The Chairperson;
ii. One (1) external lay person;
iii. One (1) external scientific person.

6.1.3 If the chairperson is absent from any meeting or part of a meeting, the Vice Chairperson or a member appointed by the chairperson or vice chairperson will preside at that meeting or part of the meeting.

6.1.4 All decisions of the PIEC shall require a simple majority vote. In the event of a tie, the research is rejected.

6.1.5 Each member must declare at every PIEC meeting the nature and the extent of all conflicts of interest or potential conflicts of interest in relation to a matter under consideration by the board at that meeting.

6.2 Possible Review Outcomes

6.2.1 Under full board review, PIEC shall make one of the decisions listed below:
Approved – The investigator is not required to change any aspect of the protocol or consent document. T
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.
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.
Suspend or Terminate Approval – There is major concern with safety.

6.3 Meeting Minutes

6.3.1 The minutes shall be in sufficient detail to show attendance at the meetings; actions taken by PIEC; the vote on these actions including the number of members voting for, against, and abstain; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

6.4 Communication to Study Team

6.4.1 Conditional Approval / Deferred - When there are queries following PIEC review, the Study team will receive a written notification that lists the clarifications and modifications required in a research proposal to secure PIEC approval. The justifications for any substantive modification will be included.

6.4.2 Approved - When an application approved by the PIEC, an approval letter will be issued. PIEC may impose additional, specific condition if deemed necessary.

6.4.3 Not Approved - If the PIEC decides not to approve a research proposal, the study team is informed of the PIEC decision in writing:

i. the date of the decision taken by the PIEC
ii. clear statement of the decision being conveyed
iii. reasons for the PIEC's decision not to approve the research proposal
iv. any advice of the PIEC
v. statement that informs the PI/Coordinating PI the avenues to respond to this letter

7 Initial Review

7.1 Criteria for Approval

7.1.1 In order to approve research covered by this policy, PIEC shall determine that all of the following requirements are satisfied:

7.1.2 **Risks Minimized**

Risks to subjects are minimized:

i. By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
ii. whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

The committee verifies that the research plan, including research design and methodology, will not place participants at unnecessary risk, considering physical, psychological, social, economic, and legal risks. This may include research that is inadequately designed or is lacking in statistical power, such that meaningful results cannot be obtained.

The committee shall also consider the professional qualifications and resources of the research team.

7.1.3 **Risks Reasonable Relative to Anticipated Benefits**

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

In evaluating risks and benefits, the committee should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The committee should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

The committee develops its risk/benefit analysis, using the component analysis of risks and potential benefits in research, by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information.

7.1.4 **Equitable Selection of Subjects**

Selection of Subjects is Equitable – In making this assessment the PIEC will take into account:

i. the purposes of the research
ii. the setting in which the research will be conducted
iii. whether prospective participants will be vulnerable
iv. the adequacy of inclusion and exclusion criteria
v. Subject recruitment and enrollment procedures
vi. The influence of payments to participants i.e. the amount and the timing of payment

The committee should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. Generally, a population that stands no chance of benefiting from the research should not be selected to assume the risk.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, but not lacking mental capacity (for example, uniformed personnel, employees or institutionalized individuals), consent should be taken by an independent third party, or if it is not possible, there should be provisions to manage the conflict of interest and sufficient safeguards to protect the welfare and interests of the subjects.

The committee should be mindful of the importance of including members of minority groups in research, particularly when the research holds out the prospect of benefit to individual subjects or the groups to which they belong.
Non-English speaking participants should not be systematically excluded because of inconvenience in translating informed consent documents. The committee should also ensure that participants are not taken from one group of people because it is convenient.

The committee should be mindful of the desirability of including both women and men as research participants and should not arbitrarily exclude the participation of persons of reproductive age. Exclusion of such persons must be fully justified and based on sound scientific rationale.

7.1.5 **Informed Consent**

Informed consent will be sought from each prospective subject or the subject's legally acceptable representative, unless a waiver of consent is approved by the committee. Any such waiver must be consistent with current applicable regulations.

i. The investigator would obtain the legally effective and freely given informed consent of the participant or the participant’s legally authorized representative.
ii. The circumstances of the consent process provided the prospective participant or the legally authorized representative sufficient opportunity to consider whether to participate.
iii. The circumstances of the consent process minimized the possibility of undue influence or coercion.
iv. The individuals communicating information to the participant or the legally authorized representative during the consent process would provide that information in a language understandable to the participant or the representative.

7.1.6 **Documentation of Informed Consent**

Informed consent will be appropriately documented, unless documentation can be waived by the committee. Any such waiver must be consistent with current applicable regulations.

7.1.7 **Plans for Data and Safety Monitoring**

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

For research in which risks are substantial, a general description of the data and safety monitoring plan must be submitted to the committee as part of the research proposal.

7.1.8 **Privacy of Participants and Confidentiality of Data**

When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Personal data used for research should be de-identified as early as possible and stored and managed as de-identified information. The level of care and urgency regarding de-identification and data protection should be consistent with the sensitivity of the data.

7.1.9 In developing strategies for the protection of subjects' privacy, consideration should be given to:

i. The methods used to identify and contact potential participants.
ii. The settings in which an individual will be interacting with an investigator.
iii. The observation of the interaction by individuals not related to the research.
iv. The methods used to obtain information about participants.
v. The nature of the requested information.
vi. The nature of the experiences related to the research.
vii. Information that is obtained about individuals other than the "target participants," and whether such individuals meet the regulatory definition of "human participant" (e.g., a subject provides information about a family member for a survey).
viii. Privacy guidelines developed by relevant professional associations and scholarly disciplines (e.g., oral history, anthropology, psychology).
ix. How to access the minimum amount of information necessary to complete the study.

7.1.10 When the committee evaluates research proposals for strategies for maintaining confidentiality, where appropriate, consideration will be given as to whether:

i. Methods to shield participants' identity adequately protect participant privacy.
ii. There is a long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data.
iii. The consent form and other information presented to potential research participants adequately and clearly describe confidentiality risks.
iv. The informed consent process and the informed consent document, and if applicable the Authorization Form, clearly delineates who will have access to the subject's information and under what circumstances data may be shared or accessed (i.e., government agencies, sponsors, IRBs, etc.).

7.1.11 **Qualification and Training of Investigator**

All investigators should possess appropriate and adequate qualifications in order to ensure proper conduct of the research.

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

i. Local registered medical practitioner, or
ii. Local registered nurse, or
iii. Healthcare Professional e.g. physiotherapist, audiologist, nutritionist, optometrist, or
iv. Scientific Researcher with at least Ph.D qualification.

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.

For studies involving more than minimal risk, the investigator has to be a local registered medical practitioner.
For trials involving medical device, the investigator has to be adequately trained to operate/use the device by submitting relevant proof of compentency to PIEC. e.g. CV, certificate of training etc.

Minimum Training requirement

All investigators must fulfil one of the following training requirements:

i. Human Subject Research (HSR) Course by Collaborative Institutional Training Initiative (CITI)
ii. Good Clinical Practice (GCP) Course by Collaborative Institutional Training Initiative (CITI)
iii. 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.

7.1.12 **Management of Conflict of Interest**

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

7.1.13 **Additional Considerations**

a. Adequacy of Research Facility

In general, a research facility should be equipped based on the type of clinical studies that is planned and the individual study protocol requirements.

PIEC may adopt a risk-based approach when assessing the suitability of the research premises, with the primary objective to ensure the safety of the subjects. For instance,

(i) where interventions involve intravenous injections, these have to be conducted within a licensed healthcare facility (as required under the Private Hospitals and Medical Clinics Act). A research unit should not be involved in treating patients if it is not a PHMC* licensed facility.

(ii) where First-in-Human Trial or other high risk trial is conducted, the research unit is required to have in place a qualified system to handle emergency situations, including time to resuscitation and transfer to the hospital emergency room. *(Note: PIEC may refer to the ABPI guidelines for phase I clinical trials or the UK MHRA phase I accreditation scheme.)*
PIEC may initiate a site inspection or request for a facility tour, when deemed necessary.

b. Adequacy of the System of Oversight

PIEC should assess whether a system of oversight is available and adequate based on the type of clinical studies that is planned and the individual study protocol requirements and whether the research institution has adequate resources to proactively monitor the conduct of the research. PIEC may stipulate that monitoring service be engaged, if such function is not available at the research institution, when deemed necessary.

8 Continuing Review

8.1 When is Continuing Review Required

8.1.1 Continuing review and re-approval of a research project at least annually is required so long as the project continues to involve human subjects.

8.2 Criteria for Approval

8.2.1 In order to re-approve research at the time of continuing review, the committee must determine that all of following requirements are satisfied:

i. Risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits;
ii. Selection of subjects continues to be equitable;
iii. Informed consent continues to be sought from each prospective subject or subject's legally authorized representative, and appropriately documented;
iv. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
v. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and
vi. Appropriate safeguards are included to protect subjects likely to be vulnerable to coercion or undue influence and the research continues to satisfy the additional requirements for approval.

8.2.2 PIEC has the authority to disapprove or require modifications in (to secure re-approval of) a research activity that does not meet the above criteria.

8.2.3 If research does not satisfy all of the above criteria, PIEC must require changes that would result in research satisfying these criteria, defer taking action, or disapprove the research.

8.2.4 The PIEC may impose special precautions or relax special requirements it had previously imposed on the research proposal.

8.2.5 If major issues affecting participants' safety are identified, PIEC shall report these incidents to the RI.

9 Review of Amendments

9.1 Administrative Change

9.1.1 Administrative changes such as contact detail updates, editorial change etc. will be reviewed by the administrator.

9.2 Minor Revision

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

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

Addition of procedures that

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

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

i. Changing the number of research participants
ii. Adding co-investigators
iii. Revising or adding of recruitment materials
iv. Minor consent form changes
v. Minor changes to recruitment procedures, recruitment materials or submission of new recruitment materials to be used in accordance with approved recruitment methods
vi. Minor changes to study documents such as surveys, questionnaires or brochures
vii. New study documents to be distributed to or seen by subjects that are similar in substance to those previously approved
viii. 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
ix. Decrease in the number and volume of sample collections as long as they do not negatively alter the risk/benefit ratio of the study
x. Editorial changes that clarify but do not alter the existing meaning of a document
xi. Addition of or changes in study personnel
xii. Addition of a new study site
xiii. Translations of materials already reviewed and approved by PIEC
xiv. Decrease in drug dosage based on current information
xv. Removal of an invasive procedure

9.3 Substantive Revision

9.3.1 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.

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

i. Significant changes in study design, such as the addition of a new subject population or the elimination of a study arm
ii. Adding or revising eligibility criteria that add a potentially vulnerable population or have impact on the research design or clinical endpoint
iii. Changes in inclusion/exclusion criteria that impact the risk/benefit ratio of the study
iv. Adding a new research site
v. Adding procedures that increases the overall risk to the subjects involved in the study
vi. Updating the consent document to include a newly identified side effect or adverse event related to the study drug
vii. Changing the drug dose or route of administration
viii. Change in the principal investigator. Refer to 3.6.
ix. Changes that adversely affect the risk/benefit ratio of the study or specifically increase the risk to subjects
x. New risk information that is substantial or adversely affects the risk/benefit ratio of the study
xi. Significant changes to the study documents to be distributed to or seen by subjects
xii. 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
xiii. New or revised financial conflict of interest management plans (e.g., change in PI or change to study design).
xiv. Any change in the facilities that could, in the opinion of the reviewer, limit the privacy or safety of a research participant, or limit the degree of confidentiality afforded data regarding a research participant.
xv. Any other type of amendment to the study that in the opinion of the Chairperson (or his/her designee) should be reviewed at a convened meeting.

9.4 Criteria for Approval

9.4.1 In order to approve amendments in research, PIEC shall determine that all of the following requirements are satisfied:

a. Risks to subjects continues to be minimized
b. Risks to subjects are reasonable in relation to anticipated benefits
c. Selection of subjects remains equitable
d. Informed consent continues to meet requirements
e. Informed consent will be documented if the proposed amendments require that research participants be notified of the amendments and their consent to be re-taken
f. Data and Safety Monitoring – risk-benefit profile remains favourable with the proposed amendments
g. Adequate provisions for protecting privacy of subjects and confidentiality of data
h. Additional Safeguards for vulnerable populations, if included.

9.4.2 In addition to these criteria, PIEC shall determine if the amendments to the study may impact the subject's willingness to continue participation in the research. PIEC shall ensure that this information is provided to the subject in an updated consent document or an addendum to the consent document.

10 Research Involving Minors

10.1 Category of Research Involving Minors

10.1.1 Category 1 – Research not involving greater than minimal risk to the children

10.1.2 Category 2 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

10.1.3 Category 3 – Research involving greater than minimal risk and no prospect of direct benefit to individual child subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

10.2 Consent in Research Involving Minors

10.2.1 In the event that the minor has sufficient understanding and intelligence:

i. For research involving minors under Category 1 or 2, consent is required from the minor and one adult parent, even if the other parent is alive, known, competent, reasonably available, and share legal responsibility for the care and custody of the child.

ii. For research involving minors under Category 3, consent is required from the minor and both adult parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

10.2.2 In the event that the minor does not have sufficient understanding and intelligence:

i. PIEC must determine that there are reasonable grounds for believing that the research cannot be carried out without the participation of the class of minors to which the minor belongs or the removal of the tissue is primarily for a therapeutic or diagnostic purpose.

ii. For research involving minors under Category 1 or 2, consent is required from at least one adult parent or guardian of the minor.

iii. For research involving minors under Category 3, consent is required from both adult parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

10.2.3 In the event that the minor lacks mental capacity:

i. PIEC must determine that there are reasonable grounds for believing that the research cannot be carried out without the participation of the class of minors to which the minor belongs or the removal of the tissue is primarily for a therapeutic or diagnostic purpose

ii. For research involving minors under Category 1 or 2, consent is required from at least one adult parent or a deputy of the minor.

iii. For research involving minors under Category 3, consent is required from both adult parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has

legal responsibility for the care and custody of the child; or a deputy of the minor, if the minor is parentless.

10.2.4 The following individuals are legal representatives under the Singapore law to consent on behalf of the minor in the following order of priority:

i. A deputy appointed under the Mental Capacity Act;
ii. Adult Parent, or if no parent (e.g. deceased);
iii. Legal Guardian.
   a. A guardian appointed under the Guardianship of Infants Act.
   b. A person to whom the care of a child is committed under the Children and Young Persons Act.

10.2.5 For research involving older children or adolescents aged 13 to 20 years old, where the minors are deemed having sufficient understanding and intelligence to enable the minor to understand what is proposed in the research, consent is obtained from both the minor and at least one adult parent or guardian of the minor. Provision should be made in the same consent document for legal representative and the child to sign.

11 Research Involving Persons Lacking Mental Capacity

11.1 Categories of Research involving Persons Lacking Metal Capacity

11.1.1 **Research involving interventions or procedures that are considered minimal risk and present the prospect of direct benefit to the individual subject.** PIEC may approve such studies if the risks are reasonable in relation to the prospective benefits. For new protocols, this is the only category of research involving surrogate consent that may be eligible for expedited review.

11.1.2 **Research involving interventions or procedures that are considered minimal risk and have no prospect of direct benefit to the individual subject, but are likely to yield generalizable knowledge about the subject's disorder or condition.** PIEC may approve such studies if it is important to advance to the scientific knowledge of a medical condition that affects the research population, and if the risks are reasonable in relation to such importance. For research in this category, the disorder, condition or factor that prevents the individual from having capacity to consent must be an intrinsic characteristic of the research population such that the research could not otherwise be conducted on subjects who have capacity.

11.1.3 **Research involving interventions or procedures that are considered a minor increase over minimal risk but present the prospect of direct benefit to the individual subject.** PIEC may approve such studies only if the risks are reasonable in relation to the prospective benefits, if the potential benefits are similar to those available in the standard clinical or treatment setting, and if the risk-benefit ratio is favorable to participants.

11.1.4 **Research involving interventions or procedures that are considered a minor increase over minimal risk and have no prospect of direct benefit to the individual subject, but are likely to yield generalizable knowledge about the subject's disorder or condition.** PIEC may approve such studies if vitally important to advance to the scientific knowledge of a medical condition that affects the research population, and if the risks are reasonable in relation to such vital importance. For research in this category, the disorder, condition or factor that prevents the individual from having capacity to consent must be an intrinsic characteristic of the research population such that the research could not otherwise be conducted on subjects who have capacity.

11.1.5 **Research involving interventions or procedures that are considered a more than a minor increase over minimal risk but present the prospect of direct benefit to the individual subject.** PIEC may approve such studies only if the risks are reasonable in relation to the prospective benefits, if the potential benefits are similar to those available in the standard clinical or treatment setting, and if the risk-benefit ratio is favorable to participants. Such ratios are less favorable when the risk is substantially more than a minor increase over minimal risk. Such ratios are more favorable when the prospect of direct benefit is more certain, or the benefit is expected to be more frequent or more significant.

11.2 Consent in Research Involving Persons Lacking Mental Capacity

11.2.1 Where the prospective research subject is an adult who lacks mental capacity and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of persons to which the adult belongs, the appropriate consent for the adult must be obtained from according to the following order of priority:

i. the donee, appointed by the adult subject before he/she lost capacity or
ii. the deputy, appointed after he/she lost capacity
iii. Next-of-kin (NOK) in descending order of priority;
   a) spouse;
   b) adult child;
   c) parent or guardian;
   d) adult sibling;
   e) any other adult named by the adult (when the adult did not lack capacity) as someone to consult on the issue of the adult being a subject.

11.2.2 For donee or deputy, there must be an express provision in the lasting power of attorney or appointment by the court that the donee or deputy is authorized to give consent for being subject in a research.

11.2.3 A person cannot be a legal representative of the subject or prospective subject if the person is a donee or deputy, and there is an express provision in the lasting power of attorney or appointment by the court that the donee or deputy is not authorized to give consent to the subject or prospective subject being a subject;

12 Informed Consent

12.1 Documentation of Consent

12.1.1 PIEC refers to MOH Guidance on the Requirement of Appropriate Consent for the Conduct of Human Biomedical Research and Handling of Human Tissue.

12.2 Elements of Informed Consent

12.2.1 PIEC may stipulate that the informed consent form submitted for a proposed research to include some or all of the following elements, where applicable.

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 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 Subjects are explicitly informed of other potential conflict of interests of the research team.

2 PURPOSE OF THE RESEARCH STUDY

2.1 A statement that the trial involves research or the investigational nature of the research

2.2 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 For adult/minor lacking mental capacity / sufficient understanding and intelligence to give consent:
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 The approximate number of subjects involved in the research (study site, Singapore and global).

2.6 The expected duration of the subject's participation in the research

3 WHAT PROCEDURES WILL BE FOLLOWED IN THIS STUDY

3.1 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 The probability for random assignment to each treatment or procedure.

3.3 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

4.1 Whether provisions is made available for post-trial access for all participants who still need an intervention **identified as beneficial** in the clinical trial.

5 WHAT IS NOT STANDARD CARE OR EXPERIMENTAL IN THIS STUDY

5.1 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 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 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 Whether the tissue will be used in restricted human biomedical research involving human-animal combinations;

6.4 Whether the tissue will be exported or removed from Singapore to a place outside Singapore;

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

6.6 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 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 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 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 Whether the research subject / the donor / the person authorised to give consent, would wish to be re-identified in the case of an incidental finding if the proposed biomedical research or future research expressly provides for such re-identification.

7 RESPONSIBILITIES OF THE SUBJECTS

7.1 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 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 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 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 When there is no intended clinical benefit to the subject, the subject should be made aware of this.

10 ALTERNATIVES TO PARTICIPATION

10.1 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 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 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 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 A statement that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled.

12.3 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 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 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 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 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 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 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 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 By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access

14.4 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 An explanation of whom to contact (and contact details) for answers to pertinent questions about the research.

15.2 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.

15.3 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 A copy shall be given to the person signing the form.

17 OTHERS

17.1 Any other information as the PEC deem necessary

13 Waiver or Alteration of Informed Consent Process

13.1 Research in general

13.1.1 PIEC may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided PIEC finds and documents 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.

13.2 Waiver of Documentation of Informed Consent

13.2.1 PIEC may waive the requirement for the Investigator to obtain written documentation of informed consent (i.e. a signed consent form) for some or all subjects if it finds any of the following:

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.

13.2.2 In cases in which the documentation requirement is waived, PIEC may require the investigator to provide subjects with a written statement regarding the research. The written statement must be reviewed and approved by PIEC.

13.3 Waiver of Consent for Research in Emergency Settings

PIEC may waive the requirement of consent for emergency research if all of the following are met:

13.3.1 The research subjects are in a life-threatening situation which necessitates intervention.

13.3.2 Obtaining appropriate consent is not feasible because:

i. the research subject lacks capacity within the time available to give consent as a result of the person's medical condition or situation; and

ii. no person who is authorised to give consent on behalf of the research subject (legal representative) is available within window period;

13.3.3 Neither the person nor the legal representative of the person nor any member of the person's family has informed any investigator of any objection to the person being a subject in the trial.

13.3.4 There is no professionally accepted standard of treatment or the available treatments are unproven or are unsatisfactory.

13.3.5 The collection of valid scientific evidence is necessary to determine the safety and effectiveness of a particular intervention or treatment.

13.3.6 Participation in the proposed research holds out the prospect of direct benefit to the research subjects.

13.3.7 PIEC determines that there is no reasonable way to identify prospectively potential trial subjects.

13.3.8 PIEC determines that the research may not practicably be carried out unless there is a waiver of requirement for appropriate consent.

13.3.9 Provision is made for an investigator of the trial who is a specialist and one specialist in the specialty relating to the research who is not conducting the trial certify in writing before using the person in the research (i.e. before enrolment) to the best of the specialist's knowledge that, 13.3.1 to 13.3.8 have been complied with.

13.3.10 Provision is made for one of the following, as the case may be:

i. the research subject is to be informed as soon as is practicable after he or she regains capacity of a full and reasonable explanation of his or her participation in the research and the consent of the person to be or to continue to be a subject in the trial is obtained; or

ii. all reasonable efforts are made to contact the legal representative of the person and inform him/her as soon as is practicable (including during the window period) of a full and reasonable explanation of the subject's participation in the research and the legal representative's consent for the person to be or to continue to be a subject in the trial is obtained.

13.3.11 At the time of submission, PIEC may request for a written certification, as appropriate, from the Principal Investigator (specialist) + 2 independent specialists that:

i. Trial needs to be conducted on subjects who are facing a life-threatening situation to determine safety/efficacy of the product;
ii. Available treatments are unproven/unsatisfactory;
iii. Reasonable prospect of direct benefit to the subjects;
iv. Potential subjects unable to consent due to their medical condition;
v. Not feasible to obtain consent from legal representative within window period;
vi. No reasonable way to identify prospectively potential trial subjects;
vii. Trial cannot practicably be carried out if consents must be obtained.

14 Appeal against the Decision of PIEC

14.1 Procedure

14.1.1 The investigator, within 30 days after the decision of disapproval issued by PIEC may submit an appeal to the Chairperson. Appeal shall be in writing and contains the rationale for the appeal.

14.1.2 Upon receipt of a written response from the Investigator, the appeal will be reviewed by PIEC at the full board meeting.

14.1.3 PIEC will carefully and fairly evaluate the PI's response in reaching their final decision. The PI will be notified in writing of the PIEC's final decision. If the study is disapproved, this letter will include the reason for the disapproval.