Research and Institutional Review Committee Review Procedures

A. Purpose

The primary purpose of the review procedures is to provide uniform standards for the review of research proposals.

B. Categories of Review

1. Full Committee Review (or Standard Review)

   All new human subject protocols require full board review unless they meet the criteria for expedited review (see Section 3 below). **Full committee review may include n**ew protocols for full board review are those which are first time submissions or have expired and the investigator wishes to re-activate the study, **or submissions previously tabled from RIRC meetings, continuing renewals, amendments/revisions. The committee will review in detail the application forms, protocol, informed consent(s), survey/questionnaire tools, and all supporting documentation. Results of the committee will be shared with investigators through correspondence within approximately 10 working days after the RIRC meeting. The letters may request additional information/clarification, request modifications, and any other conditions or reasons for their action taken.**

Review criteria
In evaluating a research project, the following are basic considerations as outlined by 45CFR46.111 in order to assess risks and benefits to research subject;

a. 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,
   ii. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
b. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
c. In evaluating risks and benefits, the IRB 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).
d. The IRB 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.
e. Benefits do not include any compensation that subjects will be paid for participating.

f. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
g. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.
h. Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.
i. When appropriate, the research plan makes adequate provisions when monitoring the data collected to ensure the safety of subjects.
j. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The RIRC may take one of four actions regarding a submission:

1. **Approval without questions/clarifications or modifications.**
2. **Conditional approval pending specific requests for clarifications or modifications. The investigator's response to RIRC letter will be reviewed and given final approval by the Chairman or his/her designee, who may request additional information or refer the response for a full committee review.**
3. **Tabled/deferred. RIRC has substantive concerns or more than minor requests for modification or clarification. Investigator responses to the RIRC letter must return for a full committee review.**
4. **Disapproval. The RIRC letter will outline justifications for disapproval.**

Investigators have the right to provide a rebuttal or request discussion with RIRC on disagreements. However, the RIRC retains the final authority for action taken.

Investigators attend RIRC meetings upon the request of the RIRC, usually to answer questions and provide clarifications to studies. Investigators must wait in the hallway until they are asked to enter the meeting room, and leave the meeting room prior to committee discussion and vote.

Investigators and other visitors may request, in advance, attendance at RIRC meetings, along with an explanation why attendance is requested. Their visit must be approved by the Chairman, and must sign a Confidentiality Agreement.

2. Exempt Review

Even though Federal regulations allow certain types of research to be exempt from review by IRBs, no research at The Queen's Medical Center or the Health Care System will be given exemption from RIRC review. Exemptions under Federal regulations will usually qualify for expedited review and approval.

3. Expedited Review

Expedited review is defined by 45 CFR 46 and 21 CFR 56.110 which allows the Chairman or his/her designee to review and approve certain types of research. Research that involves no more than minimal risk to human subjects, and involve only procedures listed in one or more of the following categories, may receive expedited review. The activities listed should not be deemed to be of minimal risk simply because they are included on the list. Inclusion on this list merely means that the activity is eligible for expedited review when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. The Chairman or designee conducting an expedited review may exercise all of the authority of the RIRC expect that they may not disapprove a study. When the Chairman or designee cannot approve the research under expedited review, the study is referre to the full committee for review. The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the expedited status. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' 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. Some of the expedited review categories may not apply to "vulnerable" populations, such as pregnant women, in vitro fertilization, children, prisoners, or mentally incompetent persons.
All expedited **approvals** by the RIRC Chairperson or his/her designee are brought to the next scheduled RIRC for general review and approval.
Expedited Review protocols must fall into one of the following categories:

a. Categories considered exempt as per 45 CFR 46.101 (b):

1. **Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.**
2. **Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) 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.**

3. **Research, involving the collection or study of existing (data that exists at the time the study is submitted) data (electronic, paper or other) include but is not limited to the following, if the information is publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or indirectly through identifiers linked to subjects.:**
    - **data registries/databases**
    - **documents**
    - **medical records**
    - **computerized records**
    - **log books**
    - **laboratory or diagnostic reports**
    - **pathological specimens**
    - **diagnostic specimens**

4. **Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are designed to study,, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternative to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.**
5. **Taste and food quality evaluation and consumer acceptance studies, (i) If wholesome foods without additives are consumed or (ii) if a food is consumed that contains a fodd 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 FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the US Department of Agriculture.**

b. Categories of Research that May be Reviewed by the IRB through the Expedited Review Procedure as published in the Federal Register.

1. **Clinical studies of drugs and medical devices only when condition (a) or (b) is met: (a) Research on drugs for which an investigational new drug (IND) application is not required (21 CFR part 312) (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of risks associated with the use of the product is not eligible for expedited review); (b) Research on medical devices for which (i) an investigational device exemption (IDE) application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.**

2. **Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows: (a) from healthy, nonpregnant adults who weigh at least 110 pounds. 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 (b) 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 no exceed the lesser of 50ml or 3ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.**
3. Prospective collection of biological specimens for research purposes by noninvasive means include but is not limited to the following:
    - hair and nail clippings in a non-disfiguring manner;
    - deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
    - permanent teeth if routine patient care indicates a need for extraction;
    - excreta and external secretions (including sweat);
    - uncannulated saliva collected either in an un-stimulated fashion or stimulated by chewing gum base 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;
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.) These include but are not limited to the following:
    - 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.

5. Research involving materials (data, documents, records, or specimens) that have been collect, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
6. Collection of data from voice, video, digital or image recordings made for research purposes. Recording made of subjects involving these techniques are de facto identifiable. The research must outline appropriate mechanisms to minimize the risks of invasion of privacy and the breach of confidentiality.
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 groups, program evaluation, human factors evaluation, or quality assurance methodologies.
8. **Continuing review of research previously approved by the convened RIRC as follows:**
    - **(a) Where (i) the reseach is permanently closed to enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or**
    - **(b) Where no subjects have been enrolled and no additional risks have been identified; or**
    - **(c) Where the remaining research activities are limited to data analysis.**
9. **Continuing review of research, not conducted under an IND or IDE where categories 2 through 8 do not apply but the RIRC has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.**

c. Other Categories

1. Research applications previously approved (within one year or less) with minor changes that impose minimal risk. Examples include, but are not limited to, the following:
    - Previously approved protocols with administrative or logistic modifications (change in personnel, addresses, phone numbers);

- Minor corrections in text of the protocol or application;
- Minor revisions in text of the consent form.

4. Emergency Use of an Investigational Drug or Device (emergency exemption from prospective RIRC approval)

   If the condition being treated is immediately life-threatening, there is no standard acceptable treatment available, and there is not sufficient time to obtain RIRC approval, emergency use of an investigational article may be used. The FDA regulations allow for one emergency use of a test article without full committee prospective RIRC review. The following activities must be carried out:

   a. Requests for use of a non-FDA approved drug or device under emergency or special circumstances for a single patient shall be submitted to either the Chairperson of the Medication Use Committee (for drugs) or to the Chairperson of the RIRC (for devices) for approval.

   b. Informed consent is mandatory unless the following criteria for an exception are present: (i)
      1. The obtaining of informed consent shall be deemed feasible unless, before use of the test article, both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:
         (a) The human subject is confronted by a life-threatening situation necessitating the use of the test article;
         (b) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from the subject;
         (c) Time is not sufficient to obtain consent from the subject's legal representative;
         (d) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.
      2. If immediate use of the test article is, in the investigator's opinion required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (1) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

   c. A full report of the subject's condition must be submitted to the RIRC within 5 working days after use. Any subsequent use of the test article must be submitted for Full Committee Review and approval.

5. Modifications to Approved Applications

Modifications to a protocol refers to any amendments, changes or modifications to an originally approved research protocol, informed consent document, or any previously approved document at The Queen's Medical Center. All modifications to the originally approved research application must be approved before they are initiated. Major modification requests are considered through a full committee review process. Minor modification requests can be approved through an expedited review process. The RIRC has the final responsibility for determining the minor or major designation. The approval of a modification to a protocol does not alter the original approval date or expiration date assigned to the original application or to the most recent continuing renewal report.
If a researcher wishes to revise study procedures that would change the purpose of the study or a change in the study population, the investigator needs to submit a new application for human subject approval.

a. A minor modification is restricted to changes that would not materially affect an assessment of the risks and benefits of the study. These may include, but are not limited to, the following:

    i. an increase or decrease in proposed human subject enrollment supported by statistical justification;
    ii. changes to improve the clarity of statements or to correct typographical errors as long as the change does not alter the content of the statement;
    iii. the addition or deletion of the principal investigator or co-investigators;
    iv. the addition or deletion of study sites;
    v. change in title or funding source;
    vi. and/or, the correction of street or email addresses, or phone numbers.

b. A major modification refers to changes that would materially affect an assessment of the risks and benefits of a study. These may include, but are not limited to, the following:

    i. broadening or narrowing the range of inclusion or exclusion criteria;
    ii. alterations in a drug dosage or route of administration;
    iii. the deletion or addition of diagnostic tests, monitoring procedures or study visits in relation to collection of information for safety evaluations;
    iv. and/or, modifying a procedure that does not change the study's purpose.

6. Continuing Renewal Status Report

The continuing review process of the research requires submission of a report at an interval determined by the RIRC (see Section C below). This progress report, Form 10, must include, but is not limited to, the following information:

- **Protocol RA# and date of initial approval.**
- **Title of Project and Principal Investigator**
- **Continuing Renewal Status Report due date.**
- **Indication if approval is requested for another year.**
- **If report is final report, list date study completed.**
- **Number of subjects since study initiation separated by QMC, Hawaii, National, and International.**
- **Number of QMC subjects since last report.**
- **Number of QMC subjects completing study.**
- **If no subjects enrolled since last approval, explain why.**
- **Number of withdrawals and reason for withdrawal by QMC, Hawaii, national, and international numbers.**
- **Number of adverse reactions with brief description of adverse reactions by QMC, Hawaii, national and international numbers.**
- **number of deaths (any death of subjects under study) separated by QMC, Hawaii, national and international numbers.**
- **Brief description of benefits.**
- **Current assessment of risks and benefits.**
- **Summary of recent literature (with each renewal).**
- **Other comments.**
- **The correct number of copies of approved current consent, and any other changes that require RIRC review and approval.**

As a courtesy to investigators, the Research Regulatory Office will send a notice and the Continuing Renewal Status Report form (Form 10) to investigators two months before the end of the approval period. The ultimate responsibility for submitting reports on time rests with the investigator. I

Any research study whose RIRC approval lapses is closed and not covered by an approved status.

7. Completion/Termination of Project

In order to formally complete a study file, the RIRC requires an official notification when a study is terminated or completed by submission of the Continuing Renewal Status Report (Form 10). If a study is terminated, the investigator needs to explain the reason for the termination. The completion/termination report must be sent within 3 months of the

completion/termination date. When data analysis is completed and a written report is written on the study's results, a copy of this report is required for the RIRC records. (If The Queen's Medical Center's name is to be included in an article being submitted for publication, the manuscript must be approved by Research Planning & Development prior to submission (See Policies and Procedures: Administrative #610-99-003).

C. Determining Studies Requiring Review More than Once a Year

The primary criterion for determining the frequency of continuing review by the RIRC is the degree of risk anticipated for a particular protocol. Risk determinations are defined below. The frequency of review will be determined when the protocol is initially approved. When studies are presented for continuing review, the RIRC may choose to alter the frequency of review depending on the experience to that point. If the rate of adverse experiences is higher than initially anticipated, the review frequency and risk level may be altered. If the rate of adverse experiences is less than anticipated, the risk level may be reduced and the review frequency may be lengthened, but not to exceed one year. Review and oversight by the RIRC may be more stringent if the investigator is non-compliant to Federal, State, local or The Queen's Medical Center's rules and regulations.

D. Risk Determinations

The risk level depends on the amount of risk that is inherent in the study compared to standard treatment.

1. Physical

    a. No risk means subjects will not be placed in potentially dangerous or harmful situations.[1]
    b. Minimal risk is where the probability and magnitude of physical harm does not exceed that encountered in ordinary life or during routine physical examinations or tests.
    c. Moderate risk is defined as a situation causing discomfort or inconvenience to the individual participating in the research study. Greater than minimal risk but has potential direct benefit or has potential to yield generalizable knowledge.[2]
    d. High risk is defined as a study where toxicity or side effects are above those of standard treatment. High risk can involve procedures which may induce a potentially harmful altered physical state or condition. Some examples of such procedures are: the removal of organs or tissues for study, reference, transplantation, or banking; the administration of drugs or radiation; the use of indwelling catheters or electrodes; or the requirement of strenuous physical exercise.

2. Psychological (Social, behavioral or legal aspects)

a. Minimal risk is defined as the probability and magnitude of psychological harm does not exceed that encountered in ordinary life or during routine psychological examinations or tests.
b. High risk is defined as procedures (such as: personality inventories, interviews, questionnaires, observations, photographs, tapes, records and stored data) that could involve a potential risk of harassment, non-insurability, unemployment, a threat to the subject's dignity, paternity suits or subjection to stigmatization, labeling, deceit, discrimination, public embarrassment, or humiliation. The information, if not kept confidential, could present psychological, social or legal risks.

3. Financial

a. No financial risk means the subject incurs no financial obligation for participation in a research study.
b. At financial risk indicates that some aspect of the research study must be paid for by the research subject.

4. Confidentiality (personal and sensitive information)

a. Minimal risks means no subject identifiers on the collected data.
b. High risks includes any information about an individual which, if known to unauthorized persons or the general public, might reasonably be expected to cause embarrassment or discomfort, jeopardize that person's prospects of employment or education, or affect his/her financial or social status.[3]

E. Assessment of Benefits

The RIRC is required to assess the benefits of all proposed research. The RIRC should assure that the anticipated benefits to research subjects and the knowledge researchers expect to gain are clearly identified. Benefits of research fall into two categories: benefits to subjects and benefits to society. [4]

1. Benefit to subjects: Research subjects may undergo treatment, diagnosis or examination for illness or abnormal conditions. This type of research can involve evaluation of a procedure that may benefit the subject by ameliorating their conditions or providing a better understanding of their disorder.

2. Benefit to society: Patients and healthy individuals may also agree to participate in research that is either not related to any illness they might have or that is related to their conditions, but not designed to provide any diagnostic or therapeutic benefit. Such research is designed principally to increase our understanding and store of knowledge about human physiology and behavior. Research that has no immediate therapeutic intent may, nonetheless, benefit society as a whole. These

benefits take the form of increased knowledge, improved safety, technological advances, and better health.