

Section 4:	REVIEW OF RESEARCH		
POLICY:	4.4 CONTINUING REVIEW		
This policy pertains to:	All research submitted to the THREB		
Responsibility for executing this policy:	The Chair of the Tri-Hospital Research Ethics Board, and institutional officials of Cambridge Memorial Hospital, Grand River Hospital and St. Mary's General Hospital		
Approval authority:	The Chair of the Tri-Hospital Research Ethics Board		
Last reviewed on:		Results:	
Effective date:	April 1, 2008	Supersedes document dated:	
Approved:			

1. PURPOSE

REFERENCES

This section describes the policy for the continuing review of research approved by the Tri-Hospital Research Ethics Board.

2. POLICY

Continuing review includes, but may not be limited to the following activities:

- Review of Annual Renewal Progress Reports
- Review of Reports of local Serious Adverse Event
- Review of Data Safety Monitoring Board (DSMB) and Sponsor-generated Safety Reports
- Review of Amendment Requests
- Review of Protocol Deviations/Violations
- Site visits and third party verification by THREB
- Review of any complaints regarding the conduct of the research

3. SPECIFIC POLICIES

3.1. Annual Renewal Progress Report

Annual Renewal Requests and Progress Reports will be required of all investigators at a frequency determined by the THREB at initial approval or subsequently by the Chair as deemed necessary. At minimum, the THREB will require a progress report once per year. Although the requirement “once per year” does not stipulate an exact time period, normally the research is to be reviewed on or before the anniversary date of the initial THREB approval, even though the research activity may not have begun until some time after that approval. [Note: For the purposes of Annual Review, the “anniversary date” of THREB approval is defined as the date of the THREB meeting at which a study

Annual Renewal Progress Report Form

TCPS Continuing review - Art. 1.13

ICH-GCP Continuing review - Sec. 3.1.4

is approved, even if approval is dependent on conditions that must later be met prior to Final Approval.]

Requests for Renewal with Annual Progress Reports must be submitted until all data have been collected and all contact with study subjects has concluded.

It is the Investigator's responsibility to ensure that Annual Renewal Progress Reports are submitted on schedule. However, THREB will assist by sending the Investigator a reminder notice approximately eight weeks before the Annual Renewal Progress Report is required. The form for the Annual Renewal Progress Report can be downloaded from our website at:
<http://www.grandriverhospital.on.ca/research/reas-ethic.cfm>.

The Annual Renewal Progress Report should be submitted at least five weeks before the approval anniversary date to ensure that appropriate THREB review takes place prior to the expected renewal date and to avoid interruption to the study.

Suspension of Project Lacking Annual Renewal Progress Report

If an Annual Renewal Progress Report is not received as scheduled, the investigator may be required by THREB to suspend the study and study enrollment until the report is reviewed and approved. If the Annual Renewal Progress Report is not received by the renewal anniversary date, a warning will be sent to the investigator with a deadline for response. If the deadline is not met, suspension of the project will be reviewed at the next full Board meeting and notice of the Board decision sent to the Investigator. Expiry of approval is not automatic, but follows on THREB notice of suspension. [Note: Sponsors may have their own timelines for Progress Reports and Annual Review and Renewal.] Once a notice of suspension is issued, no new subjects may be enrolled until THREB approval is reinstated. For clinical trials, subjects already enrolled in the study should receive appropriate medical care to ensure their safety and well-being. However, prospective research data may not be collected (except safety data) and no procedures that are being performed only for the purposes of the study may be undertaken until THREB approval is reinstated.

Criteria for Renewal

Continuing review must be substantive and meaningful; the rigor of the review shall be in accordance with a proportionate approach to ethics assessment.

Proportionate Approach – see TCPS, Article 1.13, p. 1.10; and Article 1.6, p. 1.7

In order for continuation of approval to be granted, the THREB will determine that:

- there have been no changes to the investigators, study protocol, consent form, or consent process since the last progress report unless these have been submitted as Amendments and approved.
- There is no conflict of interest, which has emerged since approval that might adversely affect the safety or well-being of study participants.
- The risk to subjects continues to be minimized and reasonable in relation to the anticipated benefits.
- The reports of Data Safety Monitoring Boards and Sponsor-generated Safety Reports are favourable for continuation of the study.
- There is no new literature that might alter the willingness of study subjects to participate.
- There have been no complaints from study subjects that require further investigation.

Annual Renewal Progress Report Content

Progress reports will include:

- the current status of the study,
- the number of subjects currently enrolled,
- the number of subjects who have completed the study to-date,
- the number of subjects who have been withdrawn at this site, with explanations,
- the results of any interim data analysis,
- the most recent Data Safety Monitoring Board report or Sponsor-generated Safety report, where applicable,
- the Investigator's assessment of the implications of any new literature on the risk/benefit ratio,
- any new conflict of interest not reported at the time of initial approval,
- a copy of the current consent form.

THREB staff will review the Consent Form currently in use to ensure that it is the most recently approved Consent document.

Possible Outcomes of Continuing Review

Annual Renewal Progress Reports may be given expedited approval by the Chair or designate as long as there have been no more than minor changes in the protocol and no evidence of any increase in risk to research participants. All expedited approvals will be reported to the full Board.

As an outcome of continuing review, the THREB may authorize continuation of the research, require that the research be modified or halted altogether. The THREB may need to impose special precautions or relax special requirements it had previously imposed on the research protocol such as frequency of monitoring, requirement for interim reports or duration of approval period.

3.2. Review of Local Serious and Unexpected Adverse Events

A serious adverse event (SAE) is any adverse occurrence or response to a drug/intervention, whether expected or not,

- that requires in-patient hospitalization or prolongation of existing hospitalization,
- that causes congenital malformation,
- that results in persistent or significant disability or incapacity,
- that is life threatening or that results in death,
- or that meets other definitions as described by sponsor.

Local Serious Adverse Event
Report Form

The THREB requires that Investigators submit in a timely manner all local SAEs using the Local Serious Adverse Event Report Form. This can be downloaded from our website at:

<http://www.grandriverhospital.on.ca/research/reas-ethic.cfm>

A Local Serious Adverse Event report will contain the following:

- A description of the event;
- The Investigator's opinion regarding its relation to the study drug/device/procedure;
- The action taken in response to the SAE;
- The outcome of the SAE;
- The Investigator's opinion regarding the implications for continuation of the study;
- The Investigator's opinion regarding the need for any change to study procedures, protocol, consent documents.

All local SAEs and all DSMB and Sponsor-generated safety reports will be reviewed by the THREB Chair, or designate. If the THREB Chair, or designate, feels that the adverse event(s) requires changes to the consent form, or that action is needed to protect the safety of research subjects due to the nature or frequency of reported serious adverse events, he/she may act immediately to suspend approval of the study in question pending review as soon as possible by the full THREB. Otherwise, the THREB Chair, or designate, will notify the Investigator that the SAE report has been accepted, and this will be reported to the THREB for ratification at its next convened meeting.

3.3. Non-local Serious Adverse Events

THREB does not review and will not acknowledge receipt of non-local Serious Adverse Events. Although it may be a requirement for some studies to submit non-local SAEs, THREB acknowledgment of receipt is not required by TCPS, GCP or Health Canada. Evaluable information regarding the safety implications of non-local events is provided to THREB by DSMB or Sponsor-generated safety reports.

If the Local Investigator absolutely requires some acknowledgment of receipt of submission of non-local SAEs, it will be provided only if the request is submitted with 1) a cover letter or form for REB stamp or signature AND 2) a self-addressed envelope.

3.4. Amendment Requests

Amendment Request Form – see Appendix

Changes in approved research may not be initiated without prior THREB review and approval except where necessary to eliminate apparent immediate hazards to human subjects.

Investigators must submit requests for changes to the THREB using the Amendment Request Form.

This can be downloaded from our website at:

<http://www.grandriverhospital.on.ca/research/reas-ethic.cfm>

Amendments must be submitted in such a way that:

- It is clear what aspects of the protocol, consent form, information sheet, and/or recruitment materials are

- affected;
- The nature of the proposed change is clearly identified;
 - The reason for each change is clear;
 - Any increase in risk or discomfort for study subjects is identified and justified;
 - Any need for change in the consent process is clearly outlined and justified.

The Investigator must indicate whether study subjects need to be re-consented.

Review of Amendment Requests that meet the criteria for minimal risk or minor change may be expedited by the Chair, or designate, and reported to the THREB for ratification at its next convened meeting. If the change represents more than minimal risk to subjects or minor change it must be reviewed and approved by the full THREB at a convened meeting.

3.5. Protocol Deviations

A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of an approved study that is not consistent with the current research protocol, consent document or study addenda.

ICH GCP Section 4 - Compliance
with Protocol

Examples of protocol deviations include:

- changes in procedures initiated to eliminate immediate hazards to study subjects;
- enrolment of subjects outside protocol inclusion/exclusion criteria, whether agreed to or not by the sponsor;
- medication/intervention errors (i.e. incorrect drug/intervention, incorrect dosage of the drug);
- unintentional deviation in specific research intervention procedures or timing of the research intervention which could impact upon the safety or efficacy of the study-related intervention or upon the experimental design;
- breach of confidentiality or privacy without a need to know, or by data exposure (computer security breach, documents left unsecured), and;
- significant deviation from the consenting process.

For protocol deviations as described above the Investigator must submit a letter to THREB

- 1) describing the deviation,
- 2) assessing its impact on the research participant

- and the study integrity, and
- 3) describing what is being done to correct the deviation or prevent a reoccurrence.

Upon receipt of the protocol deviation report the THREB Chair, or designate, will review the report and submit it to the full THREB if appropriate.

As noted in 3.4 above, the Investigator should not implement any deviation from, or changes of the protocol without prior THREB approval, except where necessary to eliminate an immediate hazard(s) to subjects, or when the change(s) involves only logistical or administrative aspects of the trials (e.g. change in monitor(s), change of telephone number(s)).

The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to subjects without prior THREB approval. However, as soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) must be submitted to the THREB for review.

3.6. Reports from Employees, and Staff

It is the responsibility of the investigative team, medical staff, nursing staff, or any other employee of the institutions to promptly report to the THREB any findings, results, occurrence, or new information about a study being conducted at any facility under the jurisdiction of the THREB that could affect the rights and welfare of research subjects. It is the responsibility of the THREB staff and members to act on any such information in order to protect research subjects.

Other Entities – see Section 602

3.7. Ensuring Prompt Reporting of any Serious or Continuing Noncompliance with the TCPS or the Requirements or Determinations of the THREB

The THREB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the THREB policies, is not in compliance with applicable regulations, or has been associated with unexpected serious harm to subjects.

Review Procedures for Ongoing Research – see TCPS, Article 1.13, p. 1.10

All credible reports to the THREB of inappropriate involvement of human subjects in research must be

investigated by the THREB Chair.

The suspension or termination of approval of research, or the results of an investigation as mentioned above will be reported by the THREB Chair to the appropriate Institutional official(s).

Regulatory authorities or sponsors may also be notified by the appropriate Institutional official(s) in accordance with applicable laws, or the terms and conditions of research agreements or contractual arrangements.

3.8. Other Monitoring Procedures

The THREB has the authority to observe, or have a third party observe, the consent process of research it has approved, and to verify that the study is being conducted within THREB Policies and Procedures. THREB personnel or members may perform site visits or use another party either affiliated with the Institution or not, to verify information in the study application, or in any interim, continuing review or renewal submissions.

Site visits, audits and consent verification may be conducted on a random basis, or for cause.

Sponsors may be asked to submit copies of monitoring reports, or may be requested to complete a questionnaire regarding the protocol and/or the investigative site.

Investigators may be asked to submit copies of signed informed consent forms or other documents to ensure their compliance with THREB requirements.

The THREB may conduct interviews with screened and/or enrolled subjects as deemed necessary.