Section 400:	**REVIEW OF RESEARCH**		
Standard Operating Procedure (SOP):	**405 ONGOING REVIEW AND REPORTING**		
This SOP pertains to:	All Research submitted to the REBs		
Responsibility for executing this SOP:	Director, Research Ethics, Research Ethics Staff, the Chairs of the University of Saskatchewan Research Ethics Boards		
Approval Authority	The Vice-President Research		
Effective Date:	July 1, 2012	**Superseded documents dated:**	

1. PURPOSE: This section describes the ongoing review and monitoring by the REO and REBs of research approved by the University of Saskatchewan REBs, after approval but not including study renewal (SOP406) and study closure (SOP407). The process for further follow up reporting of unanticipated problems, reporting of serious and continuous non-compliance (SOP 408), and suspension and termination of research (SOP 409) are described in SOP 410.	**REFERENCES** SOPs 406, 407, 408, 409 and 410
2. POLICY: It may be that the real risk/benefit ratio can be evaluated only after research has begun; therefore, in addition to the formally scheduled annual (interval) renewal, the REB must receive and review any new information generated throughout the course of the research that might affect the rights, safety and well-being of research participants. Such review may include: • Site visits • Third party verification; • Review of significant new findings or new information that may adversely affect the safety of the research participants or in the instance of Biomedical Research, the conduct of the clinical trial; • Review of serious and unexpected adverse events and unanticipated problems posing risks to participants or others; and • Review of amendments or changes to research, including protocol deviations.	TCPS2 Article 6.14 45 CFR 46.109(e) 21 CFR 56.109(f) See SOP 406 - Annual (Interval) Renewals
3. SPECIFIC PROCEDURES: 3.1 Site Visits The REBs have 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 as required by the REB and within University and site-specific Policies and Procedures as appropriate. Under the direction of the Director Research Ethics, REO	See SOPs 901 and 902

personnel or third parties not affiliated with the institution may perform site visits to verify information in the study application, or in any interim, continuing review or renewal submissions. 3.1.1 Site visits may be random or 'for cause" • Random site visits will be chosen on the basis of proportional review with research involving vulnerable populations or high risk procedures having a higher probability of being selected for a site visit • The REB will consider the following criteria to determine if a "for cause" site visit is required: • The investigator has a history of serious or continuing noncompliance related to continuing review in the past three years; • The REB has reason to doubt the veracity of the information provided by the investigator; • The information provided by the investigator is inconsistent with other information known to the REB and the inconsistency cannot be resolved through communication with the investigator; • Any other reason where the REB believes a site visit is required.	
3.2 External Verification: REBs routinely utilize sources other than the Investigator to identify information that may affect projects currently under their oversight. Those sources include but are not limited to, the Institution, including the principle Investigator's supervisor, FDA or Health Canada Inspection reports, media reports, participant complaints, research staff, site visit reports and the Internet (FDA warning letters, OHRP and FDA debarment lists and Federal Register notices.) In addition, the following avenues provide University of Saskatchewan REBs with information that is supplemental to the information provided by the investigator: • The U of S site visit/continuing review program. • U of S REBs require copies of data monitoring committee reports for review at annual (interval) renewal. • The U of S Research Ethics Office may be in direct contact with University officials responsible for handling all allegations of research misconduct and shall be notified in the event that an investigator has his or her privileges revoked or has otherwise been disciplined or investigated by the institution regarding the conduct of the research.	45CFR46 104(b)(4)(ii) 21CFR56.108(a)(2)

• U OF S's REBs may be directly contacted by research sponsors to notify the Boards of relevant information when appropriate.	
3.3 Definitions: **Unanticipated Problems**: Unanticipated problems are any incident, experience, or outcome that meet all of the following criteria: 1) Unexpected (in terms of nature, severity, or frequency) (a) given the research procedures that are described in the protocol related documents, and b) the characteristics of the population being studied; and 2) Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the drugs, devices, or procedures involved in the research); and 3) Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized, or that were not described in the original application. Unanticipated problems include anything that could significantly impact the conduct of the study or alter the REBs approval or favourable opinion to continue the study. Unanticipated problems include, but are not limited to: • Serious unexpected adverse events / drug reactions (including medical device serious adverse events); • A breach of confidentiality or privacy; • Problems with the investigator or study personnel; • Fire, flood or other natural disaster; • Incidents of continuing and serious noncompliance with the ICH-GCP, REB requirements or applicable laws and regulations; • Termination or suspension of the study by a regulatory authority • Any complaint by a participant that includes a report of an unanticipated risk or which cannot be resolved by the research staff; • Protocol deviations that in the opinion of the Investigator places one or more participants at increased risk, or affects the rights, safety or welfare of research participants; • For an "expected" serious adverse drug reaction, an increase in the rate of occurrence which is judged to be clinically important; • A significant hazard to the research participant population such as lack of efficacy with an investigational product used in treating a life-threatening disease; • A major safety finding from a newly completed animal study that suggests a significant risk for human participants (such as	OHRP Guidance on Reviewing and Reporting Unanticipated Problems 10 Nov 2010. FDA Guidance for Clinical Investigators, Sponsors and IRBs Adverse Event Reporting January 2009 U OF S Guidance notes for Request for Acknowledgement.

carinogencity); • Recommendations of the Data and Safety Monitoring Committee , where relevant for the safety of the research participants; • Protocol deviations / violations that impact data integrity or the safety of research participants.	
New Information: Any new information that might adversely affect the safety or well being of the study participants, the conduct of the trial, or the participant's willingness to continue in a study. New information includes but is not limited to any relevant recent literature, interim findings, preliminary results of the study or of any other study (e.g. using the same drug). **Adverse Event (AE**): any untoward medical occurrence in a research participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. **Non-Local (External) adverse event:** From the perspective of the REB overseeing one or more centres engaged in a multicenter research project or clinical trial, external adverse events are those adverse events experienced by research participants enrolled by investigator(s) at other centres/institutions outside the REB's jurisdiction. **Local (Internal) adverse event**: local adverse events are those adverse events experienced by research participants enrolled by the investigator(s) at one or more centres under the jurisdiction of the REB. In the context of a single-centre research project or clinical trial, all adverse events would be considered local adverse events. **Adverse Drug Reaction (ADR):** All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions. The phrase responses to an investigational product means that a causal relationship between the investigational product and an adverse event is at least a reasonable possibility (i.e., the relationship cannot be ruled out). **Serious Adverse Event/Experience (SAE) or Reaction**: any untoward medical occurrence that at any dose: • results in death	Definitions adapted from ICH-GCP E6 guidelines Definition adapted from UCH-GCP E6 Guidelines

• is life-threatening • requires inpatient hospitalization or prolongation of existing hospitalization • results in persistent or significant disability/incapacity • is a congenital anomaly/birth defect • based upon appropriate medical judgment, is an important medical event that may jeopardize the study participant or may require medical intervention to prevent one of the outcomes listed above. **Medical Device Serious Adverse Event:** An adverse event associated with a medical device complaint meets the criteria of a medical device SAE when the event involves a medical device **and** results in death or serious deterioration in state of health. "Serious deterioration in the state of health" means: a life-threatening disease, disorder or abnormal physical state; the permanent impairment of a body function or permanent damage to a body structure; or a condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage. **Unexpected Adverse Drug Reaction**: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the Investigator's Brochure for an unapproved investigational product). Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis. **As soon as reasonably possible:** The term "as soon as reasonably possible" means that the timing of reporting will vary in accordance with the severity/seriousness of the information being reported, including the nature of the research associated with the problem. Unless, however, the event is a routine safety letter, DSMB report, summary report or changes to the Investigator's brochure that are minor and/or routine in nature, **all new information and unanticipated problems must be reported within seven (7) calendar days** of the incident, occurrence, outcome event, or the Investigator's receipt of the notice of the event or the new information.	Minister of Justice Medical Device Regulation SOR98-282

Minor Changes: Changes that neither increase the risk, nor materially change the risk-benefit ratio of the research study and do not substantially change the specific aims / design of the study. **Periodic Safety Update Report:** A summary report, created at least semi-annually, by a study sponsor, listing all of the suspected unexpected serious adverse reactions (SUSARs) that have occurred in that reporting period **and** that also includes a concise summary highlighting the main points of concern and the evolving safety profile of the investigational product,	Adapted from ICHE2F Draft Consensus Guideline "Development Safety Update Report" 5 June 2008
3.4. New Information and Unanticipated Problems that are not Adverse Events and Other Events or Findings. Regardless of whether a research project is biomedical in nature or behavioural, all U OF S researchers must promptly notify the applicable REB of any information about a study that could affect the rights, safety and well-being of research participants. In general, only those incidents, experiences or outcomes that require a change to the study procedures, study documents and/or require notifying the research participants should be reported to the REB. Notification to the applicable REB of events resulting in increased or different risks must be made **as soon as reasonably possible** following the occurrence of the event. Notification and approval of changes to the research study must be made prior to the changes being implemented, unless it is a change to a protocol taken without prior REB review to eliminate an apparent immediate hazard to a research participant (or a minor logistical change such as a change in monitor or telephone contact number), in which case notification shall be made **as soon as reasonably possible** after the change has been made. Notification to the applicable REB of new information that might adversely affect the safety or well-being of the study participants or the conduct of the study must be made **as soon as reasonably possible** after the Investigator becomes aware of such information. **3.4.1. Other Events or Findings** Other events or findings that must be reported to the applicable REB include but are not limited to: • Safety letters (provided that they do not meet the definition of an SAE) • DSMB reports • Summary Reports	REB Guidelines on Request for Acknowledgement

• Changes to the Investigator Brochure • Studies on hold, off hold • Studies closed to accrual / enrollment	
3.5 Specific Requirements for Reporting Adverse Events that are Unanticipated Problems Adverse events as defined in the ICH-GCP's, Canada's Food & Drug Act Regulations, and the US Food Drug and Cosmetic Act (if applicable) occur in the context of biomedical research. Local Adverse Events: Principal Investigators must report local adverse events that are determined by the Investigator to meet the definition of an unanticipated problem as defined in Article 3.3. Local adverse events that meet the definition of an unanticipated problem must be reported to the REB as soon as reasonably possible, but in any case, **within seven (7) calendar days** of their occurrence using the Request for Acknowledgement Form. If an Investigator determines that an adverse event is not an unanticipated problem, but the sponsor subsequently determines that it is, the Investigator must report this determination to the REB as soon as reasonably possible after the Investigator becomes aware of the sponsor's determination. **Non-local (external) adverse events:** In general, Investigators and REBs are not appropriately situated to assess the significance of individual external adverse events. For multi-centre studies, the sponsor and/or data and safety monitoring committee is in a better position to process and analyze adverse event information for the entire study and to determine whether an event is both "unanticipated" and a "problem" for the study. Accordingly, U of S investigators may rely upon the sponsor's assessment and provide to the REB a periodic safety update report prepared by the sponsor. The format used for annual safety reports is acceptable. Single isolated external adverse events rarely meet the requirements for reporting to REBs. Individual external adverse events should only be reported when a determination has been made that the event meets all of the criteria for an unanticipated problem. Individual isolated external adverse events should only be reported to the REB if they are unanticipated problems and the report includes **all** of the following information: • The event described is both serious and unexpected; and • The report identifies all previous safety reports concerning similar adverse experiences; and	US Department of Health and Human Services Guidance for Clinical Investigators, Sponsors and IRBs Adverse Event Reporting, January 2009 CAREB Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada (Draft, February 2010)

• The report analyzes the significance of the current adverse experience in light of the previous reports; and • The report outlines any proposed protocol changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the unanticipated problems. Reports not meeting these requirements will be returned to the submitter with a description of the REB reporting requirements. Periodic safety update reports, individual reportable external adverse events (i.e. those that represent unanticipated problems) should be reported as soon as reasonably possible after receipt of the report or notice of the event by the Investigator.	
3.6 Content of and REB Review of Reports of Unanticipated Problems Reports of unanticipated problems shall be submitted using the Request for Acknowledgment form. Reports of unanticipated problems other than those that are adverse events shall include: • A description of the incident, experience or outcome • An explanation of the basis for determining that the incident, experience or outcome represents an unanticipated problem (as defined in 3.3.); • The Investigator's opinion regarding its causality to the study/device procedure; • The action taken in response to the unanticipated problem; • The outcome of the unanticipated problem; • 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 or consent documents. Reports of Unanticipated problems that are adverse events shall include: • A detailed description of the event and if the event is local an assessment as to whether the event reaction was mild, moderate or severe; • An opinion expressed by the investigator (if local) or the sponsor (if a qualifying reportable non-local adverse event) that the event is both serious and unexpected and a justification of that opinion; • An opinion expressed by the investigator (if local) or the sponsor (if a qualifying reportable non-local adverse event) that the event is related or potentially related to the study drug/procedure/device and an explanation of that opinion; • An opinion expressed by the investigator (if local) or the sponsor (if a qualifying reportable non-local adverse event)	

respecting the implications of the event on the continuation of the study and any further actions that may be required such as changes to the study procedure, informed consent or protocol;
- A statement of the response to and the patient outcome of the event.

3.6.1. **REB Review Process**: All SAE's, new information, unanticipated problems and other events or findings will be reviewed by the REB Chair or an appropriately qualified designee. If the REB Chair feels that as a result of the unanticipated problem, adverse event report, or any DSMB or Sponsor-generated safety report that changes are required to the consent form, or that action is needed to protect the safety of research participants due to the nature or frequency of the reported serious adverse events, the REB Chair may act immediately to suspend approval of the study in question pending review by the full REB. This will be reported to the REB for discussion at the next convened meeting of the applicable REB.

During the convened meeting, the REB will determine whether further action is required. Possible actions that could be taken by the REB include but are not limited to:

- Placing a hold on the study pending receipt of further information from the PI;
- Requesting modifications to the protocol, including the inclusion or exclusion criteria to mitigate any newly identified risks;
- Requesting modifications to the consent form;
- Providing additional information to past participants;
- Notifying current participants when such information might affect the participants willingness to continue to take part in the research and requiring that current participants re-consent for ongoing participation;
- Altering the frequency of continuing review;
- Observing the research or the consent process;
- Implementation of additional procedures for monitoring;
- Requiring additional training of the Investigator and research staff;
- Termination or suspension of the research.

If the research study is funded or supported by the US Federal government or regulated by the US FDA, the REB will notify the appropriate institutional official in accordance with SOP 410.

SOP 410

3.7. Amendments

45CFR46.103(b)(4)(iii)
21CFR56.108(a)(3)(4)

See Guidance Notes on Submission and Review of Amendments.

Changes in approved research may not be initiated without prior REB review and approval except where necessary to eliminate apparent immediate hazards to human participants or to implement minor logistical changes, such as changes to study personnel, contact information, granting status etc.

An amendment is a permanent intentional action or process that revises/amends/modifies a previously approved research protocol. If researchers are changing any part of a study, regardless of whether or not it is merely an "administrative" or "minor" change such as changes in granting status, staff personnel, contact person etc.) an amendment must be submitted.

Minor changes are defined in 3.3. above.

Amendments must be submitted using the "Amendments to Study" form. Amendments must clearly explain the following:
• What aspects of the protocol, consent form, information sheet and/or recruitment materials are affected. Revisions must be highlighted on an attached, revised document;
• The nature of the proposed change;
• The reason for the proposed change;
• Any increase in risk or discomfort for study participants and why it is required;
• Any need for a change in the consent process;
• Whether previously or currently enrolled study participants need to be re-consented;
• Whether or not the amendment meets minimal risk criteria.

3.7.1 Amendment Review Procedure

Amendments may be reviewed under the delegated review procedure at the discretion of the REB Chair, provided that the proposed changes are minor or administrative in nature, and/or the amendment does not involve increased risks to the study participants such that the study would no longer meet the criteria for minimal risk as outlined in SOP 402. If the proposed change represents more than minimal risk, it must be reviewed by the full REB at a convened meeting and must meet all REB criteria for approval.

3.7.2. The following types of amendments for previously approved studies must be referred to the Full Board for review.

- Addition of genetic testing, new genetic tests, or tissue

banking where genetic testing may, or will be performed. • Addition of an open label extension phase following a randomized clinical trial; • Emergency amendments that arise because of participant safety concerns that are submitted after implementation, and: • Significant changes to a protocol that may affect participant safety and may include (but are not limited to) a: ▪ Change in drug dosing/duration of exposure; ▪ Decrease in monitoring; ▪ Change in recruitment technique that may affect confidentiality or the perception of coercion; ▪ Change in experimental procedure or study population. • Any amendment that requires approval from Health Canada ▪ Amendments to the protocol that affect the selection, monitoring, or dismissal of a clinical trial participant; ▪ Amendments to the protocol that affect the evaluation of the clinical efficacy of the drug; ▪ Amendments to the protocol that alter the risk to the health of a clinical trial participant; ▪ Amendments to the protocol that affect the safety evaluation of the drug; ▪ Amendments to the protocol that extend the duration of the clinical trial; ▪ Amendments to the chemistry and manufacturing information that may affect the safety or quality of the drug.	Health Canada Food and Drug Act Regulations Part C – Division 5, C.05.008 Subsection 2
3.7.3. For studies that are funded or supported by the US Federal government or that are subject to the regulations of the US Food and Drug administration, only minor changes in previously approved research may be reviewed by the REB under delegated review procedures.	45CFR46110(b)(2) 21CFR56.110(b)(2)
3.8. 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 currently approved research protocol, consent document or study addenda. Examples of protocol deviations include: • changes in procedures initiated to eliminate immediate hazards to study participants; • enrolment of participants outside protocol inclusion/ exclusion criteria, whether agreed to or not by the sponsor;	ICH GCP 3.3.7 and 4.5.2. See U OF S Guidance Note for Submitting Protocol Deviations

• medication/intervention errors (i.e. incorrect drug/intervention, incorrect dosage of the drug); • inadvertent deviation in specific research intervention procedures or timing of the research intervention; • breach of confidentiality or privacy without a need to know, or by data exposure (computer security breach, documents left unsecured), and; • deviation from the consenting process. As noted in 3.7 above, the Investigator should not implement any deviation from, or changes of the protocol without prior REB approval, except where necessary to eliminate an immediate hazard(s) to participants, 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)). Should an Investigator implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to participants without prior REB approval he/she should submit, as soon as reasonably possible thereafter, a report notifying the REB of the implemented deviation or change, the reasons for it, and, if appropriate, an accompanying proposed protocol amendment(s) for review and approval, using the Request for Acknowledgement form. Deviations from or changes to the protocol to eliminate immediate hazards to the study participants must be reported to the REB within **seven (7) calendar days** of their discovery. All other deviations must be reported to the applicable REB within **15 (fifteen) calendar days** of their discovery. Protocol deviation reports must be completed and signed by the Principal Investigator/designated representative for the study concerned. The report must include at least the following content: • A description of the deviation that occurred with an explanation of the circumstances that lead to the deviation and the resulting problem. • An explanation as to whether or not the deviation compromised the scientific integrity of the study • An explanation of whether or not the deviation increased the risk or the possibility of risk for the research participant; • A description of steps taken or that will be taken to correct / address the problem resulting from the deviation, and; • A plan for ensuring that a similar deviation does not occur in the future.	

3.9 Reports from Employees, Staff and Faculty It is the responsibility of the investigative team, medical staff, nursing staff, or any other employee of this institution to promptly report to the REB any findings, results, occurrence, or new information about a study being conducted at any facility under the jurisdiction of the REB that could affect the rights and welfare of research participants. It is the responsibility of the REO administrative staff and members to act on any such information in order to protect research participants.	
3.10 Ensuring Prompt Reporting of any Serious or Continuing Noncompliance with the Requirements or Determinations of the REB The REB has the authority to suspend or terminate approval of research that is not being conducted in accordance with REB policies and procedures, is not in compliance with applicable regulations, or has been associated with unexpected serious harm to participants. All credible reports to the REB of inappropriate involvement of human participants in research must be investigated by the REB Chair and the REO. The suspension or termination of approval of research, or the results of an investigation as mentioned above will be reported by the REB Chair to the appropriate Institutional official(s). Regulatory authorities or sponsors may also be notified by the REB in accordance with applicable laws, or the terms and conditions of research agreements or contractual arrangements.	SOP 409 SOP 410