STANDARD OPERATING PROCEDURE **EXTERNAL SAFETY REPORTS - INDUSTRY SPONSORED STUDIES**	
SOP#: 6.2.4	**Original Approval Date: 3/25/13**
Version#: 1.0	**Current Revision Date: n/a**

1.0 PURPOSE/BACKGROUND

The purpose of this SOP is to define the process for managing external safety reports (i.e MedWatch, CIOMS, SUSARS, letters requiring action, or other expedited external safety reports) received from Industry Sponsors (referred to as "sponsor" throughout SOP) and how the Medical College of Wisconsin Cancer Center Clinical Trials Office (CCCTO) will report them to the IRB providing study oversight. As stated by the Food and Drug Administration (FDA) in their guidance on the topic, "the increasingly large volumes of individual adverse event reports submitted to IRBs—often lacking in context and detail—are inhibiting, rather than enhancing, the ability of IRBs to protect human subjects". The FDA considers the local investigator ultimately responsible for external safety reports, but the CCCTO delegates this task to the study sponsors, as allowed by the FDA guidance. The CCCTO considers the sponsor accountable for the process of reviewing and analyzing the significance of individual external adverse event information received by the sponsor from study sites in multi-center studies. This information is readily accessible to the sponsor and it is the sponsor that generally has more experience and expertise with the study drug. The sponsor must make the determination as to whether an adverse event meets the criteria set forth in 21 CRF 312.32(c)(1) and *clearly* communicate this to the the study staff, who will then report the event(s) to the IRB providing study oversight.

2.0 SCOPE

This SOP applies to all external safety reports detailing individual adverse events occurring in subjects enrolled in multi-center industry sponsored studies (i.e. MedWatch, CIOMS, SUSARS, letters requiring action, or other expedited external safety reports).

3.0 RESPONSIBILITY

Individuals impacted by this SOP may include:

- Study Sponsors and their designees
- Institutional Review Boards
- Study Staff

4.0 DEFINITIONS

Refer to Glossary of Terms and Definitions.

Additional definitions:

Drug: Refers to any investigational article (i.e. drugs, biologics, monoclonal antibodies, vaccines.)

External Safety Reports: Safety reports that originate from any site other than the MCW/FH, Community Memorial Hospital, or St. Joseph's Hospital sites.

Industry Sponsor: The entity that oversees the global conduct of the clinical trial, or their designated affiliates. Industry sponsor refers specifically to pharmaceutical companies, biotechnology companies, and medical device manufacturers.

5.0 ROLES AND PROCEDURES

Sponsor:

5.1 The CCCTO requires the sponsor to send qualifying reports directly to the CCCTO primary site contact and study Principal Investigator. The report must include a detailed explanation of the event or series of events determined to meet the criteria listed below, and *clearly* state that immediate action is required. The report must include the description of experiences or outcomes that meet ALL of the following criteria:

A. Unexpected (in terms of nature, severity, or frequency) given (i) the risks described in the protocol-related documents, such as the investigator's brochure, the IRB-approved research protocol, and the informed consent document, and (ii) the characteristics of the subject population being studied;
B. Related or possibly related to the investigational article (*possibly related* means there is a reasonable possibility that the experience or outcome may have been caused by the investigational article; and
C. Suggests that the clinical trial places subjects or others at a greater risk of harm than was previously known or recognized.

A list of the types of adverse experiences that the FDA believes should be considered to be *unanticipated problems* is appended to this policy.

5.2 In each written external safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports. The report should also include the implications for study conduct (i.e. requiring a change in the protocol such as revising the inclusion/exclusion criteria, new monitoring requirements, informed consent changes, or investigator brochure updates). Follow-up information about a safety report shall be submitted as soon as relevant information is available.

5.3 A copy of the updated protocol/consent investigator brochure(s) and/or pertinent study memos regarding direction to be taken by the sites for this safety report should be provided to the CCCTO Primary Site Contact and Study Principal Investigator.

Study Staff:

5.4 The CCCTO will review reports provided by the sponsor for all events that meet the above criteria (section 5.1), and will take the appropriate action(s) as required by the sponsor and the IRB providing study oversight.

5.4.1 When the IRB providing study oversight is the MCW/FH IRB, a reportable event application will be submitted to the IRB in accordance with IRB's reporting policy, and will detail the study team's action plan.

5.5. Any external safety reports received that *do not* meet the above criteria (section 5.1) will be listed on a log (provided by the sponsor) and the log will be submitted annually to the IRB providing study oversight, if requested. The log will be reviewed by the PI at the time that the IRB annual renewal is submitted to the IRB. (See MCW IRB SOP on Requirements for Reporting to the IRB and MCW IRB SOP on Continuing Progress Reports.) No further action will be taken with these reports. The reports themselves will not be submitted to the IRB, nor will the reports be stored/housed by the CCCTO. A copy of an individual report detailed on the log must be available from the sponsor upon CCCTO and/or IRB request.

6.0 REFERENCES

1.) FDA Regulation: 21 CFR 312.32 (c)(1)

2.) Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection, U.S. Department of Health and Human Services, Food and Drug Administration, Office of the Commissioner (OC), January 2009

3.) MCW IRB SOP on Requirements for Reporting to the IRB

4.) MCW IRB SOP on Continuing Progress Reports

7.0 APPENDICES

Identifying "Unanticipated Problems"

For clinical investigations of drug and biological products conducted under an investigational new drug (IND) application, FDA regulations state that:

- Investigators are required to report promptly "to the IRB… all *unanticipated problems* involving risks to human subjects or others," including adverse events that should be considered unanticipated problems (21 CFR 56.108(b)(1); 21 CFR 312.53(c)(1)(vii); and 21 CFR 312.66).

In this context, *unanticipated* or *unexpected* means that the specificity or severity of the adverse drug experience is not consistent with the investigator's brochure reviewed by the IRB; or, if an investigator's brochure was not required or not available, the specificity or severity of the adverse drug experience is not consistent with the risk information described in the general investigational plan or elsewhere in the current IRB application, as amended. *Unexpected* refers to an adverse drug experience that has not previously been observed (and included in the investigator's brochure), rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product (21 CFR 312.32(a)).

The FDA believes that only the following AEs should be considered as *unanticipated problems* that must be reported to the IRB *(FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection*, January 2009):

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report.
- Any other AE or safety finding (e.g., based on animal or epidemiological data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.

Authorized by: _____ James Thomas, Medical Director

_____ Betty Oleson, CTO Administrative Director

Revision dates:
3/25/13, v 1.0

Review dates:
3/7/14