HRH REB Unanticipated Problem Reporting – Supplementary Guidance

PREAMBLE

Over the past 10 years, the clinical research environment in Canada has grown increasingly complex. There is a growing trend for studies to be multi-site in nature, and for investigators to assume the responsibilities of Sponsor in addition to those of Principal Investigator ("Qualified Investigator" for regulated studies.)

There are other responsibilities that an Investigator may have due to the nature of the study he/she is conducting, and the nature of his/her relationship with that study (i.e. - as PI, or as a Sponsor-Investigator).

Where possible, this supplementary guidance document points to potential additional reporting and documentation requirements (see Table 1), but it is not meant to be exhaustive. It is the responsibility of the Investigator to familiarize himself/herself with, and follow, the requirements applicable to his/her study.

Regulators, Sponsors, Funders and Institutions may have different definitions and categorizations for the events covered by this REB supplementary guidance document, as well as documentation and reporting requirements. It is the responsibility of the Investigator to familiarize himself/herself with, and follow, the requirements applicable to his/her study.

DEFINITIONS

For the sake of brevity, with the exception of a few key terms, terms that are defined identically to the CAREB guidance document, OHRP guidance document, FDA guidance document or ICH GCP E6 are omitted in this section.

"Sponsor": An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical research study.[i]

"Sponsor-Investigator": An individual who both initiates and conducts, alone or with others, a clinical research study and under whose immediate direction the research procedures are carried out (including, where applicable, the investigational product being administered to, dispensed to, or used by a research participant). The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a Sponsor-Investigator include both those of a Sponsor and those of an Investigator.[ii]

ADDITIONAL REPORTING REQUIREMENT CONSIDERATIONS FOR UNANTICIPATED PROBLEMS

As noted in the main guidance document there are 4 different types of unanticipated events that may constitute Unanticipated Problems that require reporting to the HRH REB. The supplementary guidance supplied in this section is intended to assist with determining whether additional reporting requirements apply – irrespective of whether or not these events require reporting to the REB.

Additional Reporting Considerations for External (Non-Local) Adverse Events – Industry Sponsored

The HRH REB requires a sponsor generated periodic safety update report of the external (non-local) adverse events that are not being submitted individually on the HRH REB Unanticipated Problem Reporting Form.

Additional Reporting Considerations for Internal (Local) Adverse Events – Investigator-Initiated Studies

In the case of Investigator-Initiated Studies the Investigator may have different obligations as Sponsor to report the event to other participating sites, and to regulatory authorities, irrespective of whether or not the event constitutes an Unanticipated Problem under this guidance document.

Additional Reporting Considerations for External (Non-Local) Adverse Events – Investigator-Initiated Studies

In the case of Investigator-Initiated Studies, the Investigator should provide separate documentation (as Sponsor) confirming that – as Sponsor – he/she has evaluated the event and determined that it constitutes an Unanticipated Problem. This documentation should be provided with Unanticipated Problem Reporting Forms submitted to the REB, and to any other groups that require it (participating sites, regulatory authorities, funders, etc.).

Further Considerations Related to Protocol Deviation Reporting as Unanticipated Problems – All Studies

1. This guidance document does not differentiate between “protocol deviations” and “protocol violations”. All deviations from the protocol or documents annexed thereto constitute a protocol deviation; those deviations range from negligible to significant in their potential impact on research participant safety and the integrity of study data.

2. For externally sponsored studies, protocol deviations require reporting irrespective of whether a “waiver” is requested from and/or provided by the external Sponsor. In these scenarios it is always considered a protocol deviation and should be reported as per this guidance document.

If the protocol deviation in question is planned (e.g. – in the case of a “waiver” request to a sponsor) it is considered an amendment and Investigators should seek prior REB approval unless the deviation is to eliminate immediate real or perceived hazards to one or more research participants.

3. The CAREB guidance document does not explicitly mention protocol deviations, but it references – and is based on – OHRP and FDA guidance documents that do.

TABLE 1 – Reporting Requirements/Considerations for Unanticipated Events

Unanticipated Event Type	Unanticipated Problem? [Yes/No]	Sponsor Type	Multi-Site / Single-Site	Regulated? [Yes/No]	Reporting Requirements/Considerations
1. Internal AEs that do <u>not</u> constitute Unanticipated Problems					
Internal AE	N	External	Multi-Site	Y	Sponsor
Internal AE	N	External	Multi-Site	N	Sponsor
Internal AE	N	External	Single-Site	Y	Sponsor
Internal AE	N	External	Single-Site	N	Sponsor
Internal AE	N	Investigator	Multi-Site	Y	Regulators | Sites
Internal AE	N	Investigator	Multi-Site	N	Sites
Internal AE	N	Investigator	Single-Site	Y	Regulators
Internal AE	N	Investigator	Single-Site	N	None
2. Internal AEs that <u>do</u> constitute Unanticipated Problems					
Internal AE	Y	External	Multi-Site	Y	REB | Sponsor
Internal AE	Y	External	Multi-Site	N	REB | Sponsor
Internal AE	Y	External	Single-Site	Y	REB | Sponsor
Internal AE	Y	External	Single-Site	N	REB | Sponsor
Internal AE	Y	Investigator	Multi-Site	Y	REB | Regulators | Sites
Internal AE	Y	Investigator	Multi-Site	N	REB | Sites
Internal AE	Y	Investigator	Single-Site	Y	REB | Regulators
Internal AE	Y	Investigator	Single-Site	N	REB
3. External AEs that do <u>not</u> constitute Unanticipated Problems					
External AE	N	External	Multi-Site	Y	None
External AE	N	External	Multi-Site	N	None
External AE	N	External	Single-Site	Y	None
External AE	N	External	Single-Site	N	None
External AE	N	Investigator	Multi-Site	Y	Regulators | Sites
External AE	N	Investigator	Multi-Site	N	Sites
External AE	N	Investigator	Single-Site	Y	Regulators
External AE	N	Investigator	Single-Site	N	None

Unanticipated Event Type	Unanticipated Problem? [Yes/No]	Sponsor Type	Multi-Site / Single-Site	Regulated? [Yes/No]	Reporting Requirements/Considerations
4. External AEs that <u>do</u> constitute Unanticipated Problems					
External AE	Y	External	Multi-Site	Y	REB | Sponsor
External AE	Y	External	Multi-Site	N	REB | Sponsor
External AE	Y	External	Single-Site	Y	REB | Sponsor
External AE	Y	External	Single-Site	N	REB | Sponsor
External AE	Y	Investigator	Multi-Site	Y	REB | Regulators | Sites
External AE	Y	Investigator	Multi-Site	N	REB | Sites
External AE	Y	Investigator	Single-Site	Y	REB | Regulators
External AE	Y	Investigator	Single-Site	N	REB
5. Protocol Deviations					
Protocol Deviation		External	Multi-Site	Y	REB | Sponsor
Protocol Deviation		External	Multi-Site	N	REB | Sponsor
Protocol Deviation		External	Single-Site	Y	REB | Sponsor
Protocol Deviation		External	Single-Site	N	REB | Sponsor
Protocol Deviation		Investigator	Multi-Site	Y	REB | Regulators | Sites
Protocol Deviation		Investigator	Multi-Site	N	REB | Regulators | Sites
Protocol Deviation		Investigator	Single-Site	Y	REB | Regulators
Protocol Deviation		Investigator	Single-Site	N	REB | Regulators

Unanticipated Event Type	Unanticipated Problem? [Yes/No]	Sponsor Type	Multi-Site / Single-Site	Regulated? [Yes/No]	Reporting Requirements/Considerations
6. Other Unanticipated Events that do <u>not</u> constitute Unanticipated Problems					
Other	N	External	Multi-Site	Y	Sponsor
Other	N	External	Multi-Site	N	Sponsor
Other	N	External	Single-Site	Y	Sponsor
Other	N	External	Single-Site	N	Sponsor
Other	N	Investigator	Multi-Site	Y	None (unless non-compliance with regulations/laws)
Other	N	Investigator	Multi-Site	N	None (unless non-compliance with laws, e.g. PHIPA)
Other	N	Investigator	Single-Site	Y	None (unless non-compliance with regulations/laws)
Other	N	Investigator	Single-Site	N	None (unless non-compliance with laws, e.g. PHIPA)
7. Other Unanticipated Events that do constitute Unanticipated Problems					
Other	Y	External	Multi-Site	Y	REB | Sponsor
Other	Y	External	Multi-Site	N	REB | Sponsor
Other	Y	External	Single-Site	Y	REB | Sponsor
Other	Y	External	Single-Site	N	REB | Sponsor
Other	Y	Investigator	Multi-Site	Y	REB | Regulators (if non-compliance) | Sites
Other	Y	Investigator	Multi-Site	N	REB | Sites
Other	Y	Investigator	Single-Site	Y	REB | Regulators (if non-compliance)
Other	Y	Investigator	Single-Site	N	REB

<u>Table 1</u> – Supplemental Text

Important Notes:

1. In all scenarios outlined in Table 1 above, the event may require reporting to the Institution according to any applicable institutional policies or requirements (e.g. – incident reporting, privacy breaches, adverse events, etc.). It is the responsibility of the Investigator to be aware of applicable institutional policies and requirements.

2. It is good practice to log all internal adverse events and protocol deviations, due to their potential impact on the data analysis (interim and final) for a study. Should the first page of the Unanticipated Problem Reporting Form be used by the site for logging internal adverse events and/or protocol deviations, it should be attributable to the research team member who documents the event (e.g. – name printed; page signed and dated).

Term Definitions:

Under the "Reporting Requirements/Considerations" column in Table 1 above, the following is the meaning attributed to each of the groups/terms/options listed:

REB – Report the event to the REB directly using the Unanticipated Problem Reporting Form.

Sponsor – Report the event to the Sponsor directly (notify) or indirectly (log, for reference by study monitors or auditors) according to any applicable standard operating procedures, protocol requirements, contractual obligations and/or regulatory requirements.

Regulators – Report the event to all applicable regulatory authorities (e.g. – Health Canada, FDA, OHRP) or offices (e.g. – Office of the Information and Privacy Commissioner of Ontario in the event of a privacy breach).

Sites – Report the event to other research sites, according to any applicable standard operating procedures, protocol requirements, contractual obligations and/or regulatory requirements.

None – No reporting requirements (though it is up to the Investigator to perform due-diligence to ensure this is the case). This does not mean that there are no requirements to log/document the event as per any applicable standard operating procedures, protocol requirements, contractual obligations and/or regulatory requirements.

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i Adapted from the International Conference on Harmonization ICH HARMONISED TRIPARTITE GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) Current Step 4 version (including the Post Step 4 corrections) (ICH GCP). 10 June 1996

ii Ibid. Adapted from ICH GCP.

Adapted from the UHN REB Unanticipated Problem Reporting Supplementary Guidance