



Canadian Association of Research Ethics Boards (CAREB)

Draft Guidance on

Reporting of External (Non-Local) Serious Adverse Events to Research Ethics Boards

This Draft Guidance is being distributed for comment purposes only. Comments regarding this Draft Guidance should be submitted to board@careb-accr.org by November 30, 2009.

This Guidance was endorsed by the CAREB Board of Directors in August, 2009 and is directed to Health Canada and all sponsors of clinical trials in Canada (e.g., pharmaceutical and biotech sponsors, investigator-sponsors, cooperative group sponsors, CIHR, and others). Health Canada and clinical trial sponsors will have ninety (90) days to respond to CAREB on the recommendations contained herein. CAREB is a professional association of REB members and administrators, with a membership of over 250 individuals from across Canada. The CAREB Guidance is based on recommendations made by the Serious Adverse Event (SAE) Working Group that was established after a meeting held in Vancouver on April 30, 2009 in conjunction with the 2009 CAREB National Conference and Annual General Meeting. At the end of the 90-day comment period, CAREB will prepare and issue a final Guidance document and will recommend that it be voluntarily implemented by all Canadian Research Ethics Boards (REBs), at their individual discretion.

PREAMBLE: This CAREB Guidance was developed as a result of a history of discussions relating to the matter of reporting of SAEs to Research Ethics Boards, going back at least to May 2003 when Dr. Francis Rolleston and Dr. Ray Saginur (both CAREB members) created a report for Health Canada called “Management of Ongoing Clinical Safety Information (Adverse Event Reports) in Clinical Trials”. In April 2006, the European Commission finalized a guidance document that strongly recommends summary reporting of SAEs that are external to the member state, and that has been adopted by many members of the European Union (EU). In January 2009, the United States (US) Department of Health and Human Services (DHHS), the Food and Drug Administration and a number of other agencies finalized a “Guidance for Clinical Investigators, Sponsors, and IRBs on Adverse Event Reporting to IRBs – Improving Human Subject Protection”ⁱ. That guidance also strongly endorses summary reporting with some accompanying form of analysis of the events. It also confirms that single isolated adverse events rarely meet the requirements for reporting to IRBs.

As a result of on-going frustration in the Canadian REB community, together with these international developments, an open invitation forum was held in conjunction with the 2009 CAREB National Conference and Annual General Meeting in Vancouver. The forum was supported by both Health Canada and CAREB. Presentations on the current adverse event reporting system were given by two REB Chairs, the Director of a Human Research Protection Program, a Health Canada representative, as well as a representative from Pfizer and a representative from Roche. The presentations provided sponsor, REB and Health Canada perspectives on the issue, as well as information on new developments in the EU and US and the potential role for data safety monitoring boards or similar committees. A facilitated discussion followed the presentations. The approximately 70 attendees were mainly representatives from REBs from institutions across Canada (members, Chairs, managers and administrators), in addition to representatives from sponsors (Pfizer & Roche) and Health Canada (TPD).

During his presentation, the previous Chair of the British Columbia Cancer Agency (BCCA) REB summarized the BCCA REB's last two years experience with external SAEs. The BCCA REB processed approximately 14,000 reports (including initial and follow-up reports). During that time, sponsors requested approximately 200 protocol amendments for varied purposes, including, among others, modifications prompted by observation of SAEs. The REB's estimate, using experience with the number of safety-related changes associated with each amendment, is that across over 40 protocols, more than 500 individual changes were made that affect subject safety. Only some of those changes reflected observed SAEs. Others were made because of animal studies, observation of previously unrecognized drug interactions, etc. Despite reviewing 14,000 SAE reports, the BCCA REB requested changes to a protocol or consent only twice and in one of those situations, the sponsor was already in the process of making the change. The conclusion was that sponsors, without any prompting from REBs, make a lot of safety-related changes.

The outcome of the subsequent discussion was agreement that the current system of reporting is not working, does not enhance participant protection, and in fact may be hindering the REB's capacity to review and respond to safety issues in a timely fashion which ultimately may be harming research participants. This issue has been discussed for years without any resolution, and there was agreement that action must now be taken. The attendees agreed that a working group should be formed to develop a position statement reflecting REB concerns that could be sent to Health Canada and to RX&D (to distribute to its members organizations) and to other clinical trial sponsors, after being approved by CAREB.

SAE Working Group:

Raphael Saginur, MD - Chair, Ottawa Hospital REB
Richard Neuman - former Co-Chair, Human Investigations Committee, Memorial University
Marianne Vanderwel - Director, Human Research Protection Program, IRB Services
Joe Connors, MD - BC Cancer Agency & former Chair BCCA REB
Ann Ferguson - Chair, BC Interior Health REB
Suzette Salama - Vice-Chair, Hamilton Health Sciences REB; REB member, OCREB
Laurel Evans - Associate Director, Research Ethics UBC
Janet Manzo - Executive Director, Ontario Cancer Research Ethics Board (OCREB)

BACKGROUND: The International Conference of Harmonisation (ICH) Good Clinical Practice Guidelines and US Federal Regulations require Research Ethics Boards to have written procedures. Written procedures are required for conducting initial and continuing review of clinical trials, for determining the frequency of continuing review as appropriate, and for requiring that clinical trial investigators report to the REB in a variety of different situations. These include protocol deviations, changes increasing the risk to subjects and/or affecting the conduct of the trial, all adverse reactions that are both serious and unexpected, new information that may adversely affect the safety of the subjects or the conduct of the trial, and in the case of the US regulations, all “unanticipated problems”.

As a result of the interpretation of these requirements by clinical trial sponsors and investigators, Canada’s REBs are receiving thousands of reports of various incidents, outcomes and events, many of which do not meet the criteria stipulated by both the ICH-GCPs and the US regulations, of being serious, unexpected and related or possibly related to the study drug or procedure. The US Food and Drug Administration has recognized that “in particular, the practice of local investigators reporting individual unanalyzed events to IRBs, including events from all centers in a multi-center study, often with limited information and without any explanation of how the event represents an ‘unanticipated problem’, has led to the submission of large numbers of reports to IRBs that they cannot adequately assess”ⁱⁱ.

CAREB hosted an open forum on New Developments in the Management of Adverse Event Reporting in Vancouver on April 30th, 2009. This forum was attended by approximately 70 REB chairs, members, managers and administrators representing REBs and institutions across Canada, in addition to representatives from sponsors and Health Canada. The consensus reached during that forum was that the current system of reporting individual adverse event cases (including initial reports and any follow up reports) to REBs in Canada is not supportive of the REBs’ mandate of conducting ongoing review of research studies and to requiring appropriate changes to study procedures and/or notifications to participants of increased or different risks resulting from participation in such studies. Moreover, it was agreed that the current system as it relates to REBs is a “pretend system”, in that it does not provide protection to participants in clinical trials; further, in that it is wasting REB time and resources, and may be creating actual harm by negatively affecting REBs’ capacity to review and respond in a timely manner to actual situations where participant rights, welfare or safety are threatened.

GUIDANCE: CAREB endorses the SAE Working Group recommendation that all Canadian REBs develop written procedures that support an organized move to reporting of most adverse events in the form of periodic summary reports, accompanied by information that is meaningful and of use to the REB. The contents of the report would ordinarily be at a minimum: a sponsor analysis of the significance of the adverse event or perhaps such an analysis from an independent Data Safety Monitoring Board (DSMB), with a discussion of previous similar events (where appropriate). CAREB also endorses the recommendations that the written procedures further stipulate that individual case reports will be accepted only in the exceptional circumstances noted in the January 2009 US DHHS Guidanceⁱⁱⁱ as follows:

“The major exceptions to the general rule that an isolated event is not informative are serious AEs that are uncommon and strongly associated with drug exposure such as angioedema, agranulocytosis, anaphylaxis, hepatic injury, or

Stevens Johnson syndrome... Similarly, one or a small number of serious events that are not commonly associated with drug exposure, but are otherwise uncommon in the study population (e.g. tendon rupture, progressive multifocal leukoencephalopathy) should be considered an unanticipated problem involving risk to human subjects.”

Individual case reports meeting the above criteria are acceptable, but such reports must contain a sponsor analysis of the significance of the event or perhaps such an analysis from an independent DSMB, and if applicable, a corrective action plan.

CAREB endorses the recommendation that REBs refuse to accept or acknowledge receipt of non-local (external) SAEs that do not meet all of the above-noted criteria.

CAREB recognizes that for multicentre studies, the sponsor (or preferably an independent DSMB) is in a better position to process and analyze adverse event information for an entire study, and to assess whether an occurrence is both serious and unexpected. Accordingly, CAREB endorses the recommendation that REBs develop written procedures allowing for direct reporting of such information to the REB by study sponsors involved in multicentre research.

In summary, CAREB endorses the following recommendations:

- Instead of individual isolated reports, that Canadian REBs require periodic summary reports of external (non-local) SAEs that are accompanied by some form of analysis/context setting and where appropriate, suggested changes to the study; and
- Except for rare circumstances, that Canadian REBs no longer accept individual external (non-local) SAE reports. In those rare instances, the REB should require that the individual reports be accompanied by the sponsor analysis (or preferably from an independent DSMB if possible) of the significance of the event, and if applicable, a corrective action plan; and
- That Canadian REBs put in place written Standard Operating Procedures (SOPs) to manage the receipt and review of the new external (non-local) SAE process.

CAREB further endorses the recommendation that Health Canada undertake a review of the Food and Drug Act in regard to adverse events in clinical trials, bearing in mind the need for expertise, independence and technical tools to identify, interpret and act on adverse events in timely fashion. Requirements for minimum standards for content of adverse event reports and the role of data safety monitoring boards should be addressed.

^{i, ii, iii} Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting, January, 2009, endorsed by the following agencies: US Department of Health and Human Services, Food and Drug Administration, Office of the Commissioner, Center for Drug Evaluation and Research, Center for Devices and Radiological Health, Good Clinical Practice Program]