



Canadian Association of Research Ethics Boards History of the Development of the Guidance on Reporting of Unanticipated Problems including Adverse Events to Research Ethics Boards in Canada

1. BACKGROUND

The International Conference of Harmonisation (ICH) Good Clinical Practice Guidelines (GCP) and US Federal Regulations require Research Ethics Boards (REBs) to have written procedures for its activities including, for conducting initial and continuing review of clinical trials, for determining the frequency of continuing review, and for requiring that clinical trial investigators report to the REB in a variety of different situations. This “reporting to REBs” includes reporting of protocol deviations, of changes increasing the risk to subjects and/or affecting the conduct of the trial, of all adverse reactions that are both serious and unexpected, of 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, of all “unanticipated problems”. As a result of the interpretation of these requirements by clinical trial sponsors and investigators, 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 GCP and the US regulations, of being serious, unexpected and related or possibly related to the study drug or procedure.¹ There is no Health Canada regulation for reporting external adverse events to the REB. ICH requirements will be met if unanticipated problems are reported to the REB as described in the CAREB guidance document.²

In April 2006, the European Commission finalized a guidance document that strongly recommends summary reporting of serious adverse events (SAEs) that are external to the member state, and that has been adopted by many members of the European Union (EU).³ In January 2009, the United States (US) Department of Health and Human Services (DHHS), the US Food and Drug Administration (FDA) 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*”⁴. The guidance 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.

¹ The FDA regulations require reporting to **investigators** of IND Safety Reports of serious unexpected events associated with the use of an investigational product. This reporting is relevant to investigators who may encounter subjects with similar experiences in the clinical trial. Not all of these events meet the criteria for reporting to the REB as described in this guidance.

² ICH E2A, II.A.1 indicates that expedited reporting is required for serious unexpected ADRs from clinical trials as well as spontaneous or other sources. ICH E6, 5.17 notes that the sponsor should expedite the reporting of these reports to IRBs [in accordance with ICH E2A] **where required**. There is no Health Canada requirement for this; therefore these reports do not need to be sent to the REB unless they meet the definition of unanticipated problem as described in the CAREB guidance document.

³ European Commission. *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use*. April 2006.

⁴ US Department of Health and Human Services. *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting*, January, 2009.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079753.pdf

The FDA 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.”⁵

In its *Guidance on Reviewing and Reporting Unanticipated Problems*, the US Office for Human Research Protections (OHRP) under the DHHS similarly notes that “Investigators and IRBs at many institutions routinely receive a large volume of reports of external adverse events experienced by subjects enrolled in multicenter clinical trials. These external adverse event reports frequently represent the majority of adverse event reports submitted by investigators to IRBs. OHRP notes that reports of individual external adverse events often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unexpected, are related or possibly related to participation in the research, or suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. OHRP advises that it is neither useful nor necessary under the HHS regulations at 45 CFR part 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an unanticipated problem.” The OHRP guidance also notes that “...the vast majority of adverse events occurring in human subjects are not unanticipated problems.”⁶

2. THE CANADIAN EXPERIENCE

Some of the earliest documented work on this issue in Canada dates back to the late 90’s, when the Medical Research Council (MRC), the predecessor to the Canadian Institutes for Health Research (CIHR), struck the *MRC Task Force on Research Ethics Boards and Clinical Trials*. However, the Task Force was unable to find a workable solution to the management of adverse event reporting. CAREB also has a long history of working to resolve the concerns with the reporting of adverse events. In May 2003, Dr. Francis Rolleston and Dr. Raphael (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 2005, CAREB established a committee to examine the suitability of employing the Council for International Organizations of Medical Sciences (CIOMS) VI guidelines to address the burden of adverse event reporting. Dr. Rolleston and Dr. Richard Neuman produced the committee report in 2007. One recommendation was to have CAREB “work with Health Canada and Canada’s Research-Based Pharmaceutical Companies (Rx&D) to explore mechanisms fostering adoption of the CIOMS VI recommendations to eliminate routine expedited case reporting by sponsors to investigators and REBs and replace it with a system of regular evaluations of the evolving risk/benefit profile as the trial proceeds.” No changes came about as a result of either report. More recently, Roche has been working through individual institutional REBs to promote the adoption of periodic summary adverse event reporting. It is clear is that the management of adverse event reporting is a longstanding national problem warranting a national solution.

⁵ European Commission. *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use*. April 2006.

⁶ Office for Human Research Protections (OHRP) and Department of Health and Human Services (HHS) - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* www.hhs.gov/ohrp/policy/AdvEvtGuid.htm

As a result of on-going frustration in the Canadian REB community, together with the international developments on adverse event reporting, in 2009, Dr. Saginur contacted representatives from Health Canada and Rx&D to press for a meeting of interested stakeholders. As a result of this initiative, CAREB hosted an open forum on New Developments in the Management of Adverse Event Reporting on April 30th, 2009, in conjunction with the 2009 CAREB National Conference in Vancouver. The forum was financially supported by both Health Canada and CAREB. Approximately 70 REB chairs, members, managers and administrators representing REBs and institutions across Canada, as well as representatives from two pharmaceutical sponsors and from Health Canada attended the forum.

Two REB Chairs, the Director of a Human Research Protection Program, a Health Canada representative, as well as representatives from both Pfizer and Roche presented on the current adverse event reporting system. 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.

During his presentation, the former Chair of the British Columbia Cancer Agency (BCCA) REB summarized the BCCA REB's last two years experience. Over those two years, the BCCA REB processed approximately 14,000 external SAE 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 and that investigators and REBs - as pointed out in the OHRP Guidance - "...are not appropriately situated to assess the significance of individual external adverse events. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol."⁷

A facilitated discussion followed the presentations. The overall conclusion was that the current system of adverse event 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. 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. The forum attendees noted that this issue has been discussed for years without any resolution, and there was agreement that action must now be taken.

⁷ Office for Human Research Protections (OHRP) and Department of Health and Human Services (HHS) - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* www.hhs.gov/ohrp/policy/AdvEvtGuid.htm

3. ACTION TAKEN

The attendees at the forum recommended the creation of a SAE working group that would draft a document reflecting REB concerns. Once approved by CAREB, the plan was to distribute the document to Health Canada and to Rx&D (to distribute to its member organizations) and to other clinical trial sponsors. Volunteers came forward to join the working group.

The SAE Working Group met a number of times over the summer and ultimately created a draft guidance document for CAREB review, which the CAREB Public Affairs Committee and the CAREB Executive subsequently endorsed. On August 21, 2009, the Board of Directors of CAREB issued its *Draft Guidance on Reporting of External (Non-Local) SAEs to Research Ethics Boards in Canada* for a 90-day consultation period (ending November 30). The Draft Guidance was broadly distributed - to the research ethics community, the biomedical research community, biomedical networks, clinical trial sponsors and Health Canada.

CAREB recommended 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. It was also recommended that requirements for minimum standards for the content of adverse event reports and the role of data safety monitoring boards be addressed.

4. OUTCOME

Fourteen responses were received from multiple stakeholders including pharmaceutical and cooperative group sponsors and research ethics boards (REBs). Health Canada did not respond, although they did acknowledge receiving the draft Guidance. In general, the responses were favourable and the recommendations were constructive (e.g., to provide clear terms and definitions, to provide operational guidance to facilitate standardization across Canada, to harmonize with ICH E2F and with EU and US requirements, to apply the same principles and processes to both local and external SAEs, and to obtain Health Canada endorsement).

The CAREB SAE Working Group (WG) incorporated the comments received during the public consultation into a revised Guidance document. In revising the Guidance document, the WG referenced existing REB policies, as well as guidance documents developed by the EU, ICH, OHRP and FDA. In an effort to harmonize the Guidance with existing ones, “*unanticipated event*” and its definition was adopted as the term to describe events, incidents, experiences, or outcomes requiring reporting to the REB. This led to a broadening of the CAREB Guidance document to cover all *unanticipated events* including adverse events (both internal and external).

There were preliminary conversations with three Health Canada representatives (Siddika Mithani, Agnes Klein and Peter Monette) in December 2009 and January 2010. Health Canada noted that it “is currently conducting a policy review of the serious adverse event reporting process in the context of research ethics boards. The review will consider Health Canada's legal, regulatory and policy framework, current initiatives underway in the Department, key challenges, and options for moving forward.”

In order to provide Health Canada with another opportunity to respond, at CAREB's request, a meeting took place on February 20, 2010 with representatives from Health Canada's Bioethics, Innovation and Policy Integration Division / Science Policy Directorate / Strategic Policy Branch and the Clinical Trials/ Adverse Drug Reaction Unit as well as representatives from the CAREB

SAE WG. Health Canada committed to some form of response to CAREB within two months; however, by the time of the annual CAREB conference (May 1 & 2, 2010), Health Canada could only confirm that its policies were still being reviewed.

The CAREB Working Group subsequently met on May 25, 2010. The working group members agreed that the guidance document did not appear to contravene Health Canada regulations, the latest version of either the revised draft Tri-Council Policy Guidelines or the draft Canadian General Standards Board Standard for REBs Overseeing Biomedical Clinical Trials, and therefore recommended that CAREB issue the final guidance document without waiting for a response from Health Canada.

On June 29, 2010 Health Canada issued its response to CAREB. The response notes that Health Canada does “not have jurisdiction over how REBs conduct their operations or establish standard operating procedures.” Although Health Canada indicated that it is not their “role to endorse or take a position on external guidances”, the response suggests that Health Canada does not object to the CAREB guidance document, providing that it does not negatively impact the REB “...responsibility to ensure the protection of the rights, safety and well-being of clinical trials subjects.”

The CAREB Working Group reviewed the Health Canada response and again recommended that CAREB issue the guidance document. At a meeting on July 6, 2010, the CAREB Board of Directors approved the working group recommendation to issue the guidance document.⁸

CAREB SAE Working Group Members:

- Joseph M. Connors - former Chair, University of British Columbia – British Columbia Cancer Agency REB
- Laurel Evans - Associate Director, Research Ethics, University of British Columbia
- Ann Ferguson - Chair, British Columbia Interior Health REB
- Janet Manzo - Executive Director, Ontario Cancer Research Ethics Board (OCREB)
- Richard Neuman - former Co-Chair, Human Investigations Committee, Memorial University, Newfoundland
- Raphael (Ray) Saginur - Chair, Ottawa Hospital REB
- Suzette Salama - Vice-Chair, Hamilton Health Sciences REB
- Marianne Vanderwel - Director, Human Research Protection Program, IRB Services

⁸ Canadian Association of Research Ethics Boards. *Guidance on Reporting of Unanticipated Problems Including Adverse Events to Research Ethics Boards in Canada* July 2010