

**An Investigator's or REB's "Duty" to Share New Clinical Trials Information  
with Regulatory Authorities: Results of Research and Points to Consider**

---

*Contours of the Duty to Share Information: Selected Norms*

To help structure the Committee's reflection on the precise content of the duty to share timely information, the Table below illustrates the kinds of norms upon which it has drawn to develop advice. The table collects excerpts of selected national and international policies and legal documents that outline responsibilities relevant to an investigator's duty to share new information, including risk/benefit data, from the clinical trial process.

For instance, practically to be most comprehensive and consistent with Recommendation 1 of the CAUT report, an investigator's duty to share would begin with, be active during, and even continue after the trial. The norms excerpted in the table address these different sequences, even if they are not identical in their details.

**The Duty to Share Information in  
Clinical Trials: Selected Norms**

	WHAT	WHEN	TO WHOM / BY WHOM	BASIS
<b>CANADA: TCPS<sup>9</sup></b>	<ul style="list-style-type: none"> <li>- Participants to be given “continuing and meaningful opportunities for deciding whether... to continue to participate.”</li> <li>- “New information” for informed participation</li> <li>- Monitoring “unexpected adverse events”</li> </ul>	<ul style="list-style-type: none"> <li>- Ongoing</li> <li>- Ongoing (implied)</li> <li>- Not specified, but presumably ongoing</li> </ul>	<ul style="list-style-type: none"> <li>- To participants, by the researcher</li> <li>- To participants, by the researcher</li> <li>- To the REB, by the investigator</li> </ul>	<ul style="list-style-type: none"> <li>- Informed consent, art. 2.4(d)</li> <li>- Continuing consent commentary, art. 2.4, p. 2.6</li> <li>- Clinical trials commentary, art.7.1, p. 7.4</li> </ul>
<b>CANADA: MRC ‘87<sup>10</sup></b>	“Apparent risks” beyond those predicted	Immediately	To the REB, by the investigator	Researcher’s “accountability”
<b>CANADA: Clinical Trial Regulations<sup>11</sup></b>	“Serious unexpected adverse drug reactions” (i.e., requiring hospitalization, causing disability, life threatening or death)	15 days, if event not fatal or life threatening; 7 days, if fatal or life threatening; complete report 8 days after notification	To Health Canada, by the sponsor	Federal Drug Testing Regulations, on the basis of federal drug safety law
<b>CIOMS<sup>12</sup></b>	<ul style="list-style-type: none"> <li>- “Material changes”; new information – from the study or other sources – about risks and benefits. (Guideline 4)</li> <li>- “Significant changes” in conditions or procedures, or new information that could affect willingness to participate.</li> </ul>	Promptly (Guideline 4)	<ul style="list-style-type: none"> <li>- To participants, by investigators (Guideline 4);</li> <li>- To REBs (Guideline 4), by sponsors, if results not to be disclosed to subjects and investigators</li> <li>- To data safety monitoring board, by investigators</li> </ul>	Consent, initial and continuing

<sup>9</sup> Canada. *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, 1998.

<sup>10</sup> Canada. Medical Research Council, *Guidelines on Research Involving Humans*, 1987 (superseded by TCPS).

<sup>11</sup> Canada. *Food and Drug Regulations*, Part C, Division 5, s. C.05.014.

<sup>12</sup> Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, 2002.

	WHAT	WHEN	TO WHOM / BY WHOM	BASIS
<b>European Union<sup>13</sup></b>	- All “adverse events” to sponsor (art. 16) - Notification of serious adverse reaction to competent authorities in Member States concerned, and to ethics committee (art. 17)	- Immediately for adverse events, unless otherwise specified in investigator’s brochure (art 16) - 7 days for life threatening “serious adverse reactions,” - 15 days if non-life threatening	- To the sponsor, by the investigator; - To Member States concerned and the ethics committee, by the sponsor	Articles 16 and 17: Notification of “adverse events” and “serious adverse reactions”
<b>ICH<sup>14</sup></b>	- Serious adverse events - Unexpected serious adverse events	Immediately	- To sponsor, by investigator, unless investigator brochure states otherwise; - To regulatory authorities and REB by investigator, as per applicable regulations	Investigator safety reporting
<b>U.S. FDA<sup>15</sup></b>	- Changes in research activity and unanticipated problems involving risk, for the IRB; - Significant new findings in a trial, for participants	Promptly (to IRB); unspecified (to participants)	To ethics review committee and participants, by the investigator	Federal Drug Testing Law: standards on ethics review and informed consent
<b>U.S. HHS<sup>16</sup></b>	Unanticipated problems involving risks	Promptly	To IRB, institution’s officials and U.S. Department of Health, by the investigator	Federal Research Law, Standards on Institutional Written Procedures
<b>HELSINKI<sup>17</sup></b>	“Monitoring information . . . especially any serious adverse events.”	Not specified (presumably during the research to an ongoing trial)	To ethics review committee, by the investigator	Ethical review duties

<sup>13</sup> European Union. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001, on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.*

<sup>14</sup> International Conference on Harmonisation, (ICH). *Good Clinical Practice Consolidated Guideline*, 3.1.2, 4.8.10, 4.11.1 et seq.

<sup>15</sup> United States, Food and Drug Administration, 21 CFR 312.66 [review]; 21 CFR 50.27(b)(5)[consent].

<sup>16</sup> United States, Department of Health and Human Services, 45 CFR 46.103(b)(5).

The following (i) summarizes research on whether existing norms outline an investigator or research ethics board (REB) duty to report to regulatory authorities “new information” that arises in clinical trials, and (ii) summarizes sample points to consider on why the TCPS might include such a duty. The focus is on new risk-benefit information.

The issue raises the question of who should report what precise kinds of information to whom. A review has been undertaken of existing regulations in Canada, the United States and the European Union, the International Conference on Harmonization (ICH) and leading international documents. The research indicates that usually such norms are silent on the duties of investigators vis-à-vis regulatory authorities. The norms do outline standards governing the reporting of adverse events, amendments to protocols, compliance issues, and the sharing of new information. Most duties to report to regulatory authorities fall on sponsors/companies and concern reporting of adverse events. Some standards outline an investigator’s duty to report adverse events to sponsors; and some impose a duty on REBs/institutions to report to regulatory authorities cases of non-compliance, the termination or suspension of a trial/REB approval, or unanticipated problems involving risks.

## **I. Sample of Existing Standards**

### ***Canada: Clinical Trial Regulations***

Canadian drug legislation outlines a regulatory scheme for the licensure of new therapeutic products like medical devices or new drugs. To ensure the safety and efficacy of the latter, federal regulations have been adopted under the legislation to govern the clinical trials process for testing new drugs. Under the drug testing regulations adopted under the federal *Food and Drugs Act* (Food and Drug Regulations, Part C, Div. V, sec. C.05.014), which underwent review in 2006, “sponsors” have a duty to report to Health Canada adverse events information arising from clinical trials. “Sponsors” include any “individual, corporate body, institution or organization that conducts a clinical trial.” Usually, the sponsor is the drug company. In some instances, a researcher may be considered the sponsor, as in so-called “investigator-initiated clinical trials.” (sec. C.05.01). If so, then the duties required of sponsors would also be required of the investigator. The regulations specify that Health Canada be informed of *serious unexpected adverse reactions to drugs, protocol amendments, and suspension or cancellation of trials*. Thus, unless researchers qualify as “sponsors,” they do not currently have a duty to report information to Health Canada. Nor are REBs required to report information.

As a matter of policy, Health Canada has also adopted the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice: Consolidated Guideline (ICH-GCP), which is outlined below.

### ***Canada: Special Access Programme-Drugs***

Formerly known as the Emergency Drug Release Program, the Special Access Programme for Drugs (SAP) enables physicians to seek urgent use of an unapproved drug from Health Canada for treatment. See Health Canada, *Draft Guidance for Industry and Practitioners, Special Access Programme for Drugs*, Jan. 2007. These compassionate-use releases are regulated by federal drug law; they are not considered clinical trials.

The regulations impose a duty on practicing physicians who receive SAP authorizations to report adverse reactions to federal regulators. The duty has been central to some prominent disputes concerning reporting to regulatory authorities. In the Olivieri affair, for instance, some use of the drug under study was continued under the then equivalent SAP program, after one of Olivieri’s clinical trials was terminated. Dr. Olivieri relied on that legal duty to share with Health Canada her findings on “sustained loss of efficacy” of the drug in some patients (See CAUT, pp. 153-63). She did so over the protestations of the drug company. The regulations provide as follows:

---

<sup>17</sup> World Medical Association, *Declaration of Helsinki* (2000), guideline 13.

The Director may issue a letter of authorization authorizing the sale of a quantity of a new drug for human...use to a practitioner...for use in the emergency treatment of a patient under the care of that practitioner, if ... the practitioner has agreed to i) report to the manufacturer of the new drug and to the Director on the results of the use of the drug in the medical emergency, including information respecting any adverse reactions encountered... (Food and Drug Regulations, Part C, Div. 8, sec. C.08.010.1).

***International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice: Consolidated Guideline (ICH-GCP), 1996***

ICH-GCP article 3.3.8 provides that investigators report promptly to their REBs serious and unexpected adverse events. The article and the ICH-GCP in general are silent on any duty of REBs to report to regulatory authorities. Article 4.11.1 provides that investigators should comply with any applicable regulatory requirements relating to the reporting of serious and unexpected adverse drug reactions to regulatory authorities. Since Canadian regulations are silent on this issue, investigators are not required to report to regulatory authorities.

***European Union (EU): Clinical Trials Directive (2001/20/EC), 2001***

The Directive makes no reference to the REB or investigator duties to notify regulatory authorities. Rather, it outlines sponsor or investigator duties to report serious adverse events or amendments. For instance, under the Directive, sponsors have a duty to report serious unexpected adverse reactions of a fatal or life-threatening nature to the competent regulatory authorities in the relevant country (art. 17). Investigators have a duty to report serious adverse events to the sponsor (art. 16). The Directive also obliges sponsors to notify authorities and ethics committees of significant amendments to a trial protocol; “significant” includes concerns about participant safety (art. 10).

***Council for International Organizations of Medical Sciences (CIOMS): International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002***

CIOMS guidelines are silent on the issue of the researcher or REB reporting information during clinical trials. The only reference made to REB reporting to regulatory authorities is in the commentary to the guidelines. It states that ethics committees should be “required to monitor the implementation of an approved protocol and its progression, and to report to institutional or governmental authorities any serious or continuing non-compliance with ethical standards as they are reflected in protocols that they may have approved or in the conduct of such studies.” This may mean that ethics committees may have a duty to report investigator non-compliance—such as adverse events not being duly reported—but ethics committees are not required to report the adverse event itself.

***World Health Organization (WHO): Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000***

WHO’s guidelines indicate that ethics committees should establish a procedure for the follow-up of ongoing trials. The only specification with respect to reporting information is that serious and unexpected adverse events related to a trial or product require a follow-up review by an ethics committee that can confirm, modify, suspend or terminate the ethics committee’s initial approval of the trial. An ethics committee or investigator reporting to regulatory authorities is *not* specified.

***United States Regulations: Department of Health and Human Services—Federal Common Rule (US 45 CFR 46.103.a, and b.5)***

U.S. regulations make indirect reference to a duty to report new information to regulatory authorities. The regulations do so by requiring institutions to develop written procedures on the prompt reporting, within the institution and to regulatory authorities, of such information as “unanticipated problems involving risks” to participants. The regulations tend to specify to whom the information is to be

reported, but remain less clear on who reports the information to the regulator. The regulations thus leave within institutional discretion whether its written procedures will specify regulatory reporting by the REB, investigators, particular institutional officials, etc. The U.S. Office for Human Research Protections (OHRP), however, indicated in a recent interpretive guidance that it is the institution that reports such unanticipated problems to the Department of Health and Human Services. OHRP also indicated that, in practice, it is often the principal investigator who begins the chain of reporting. The regulations are clearest on what the written procedures must address:

“Assurances applicable to federally supported or conducted research shall at a minimum include: ... Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.” (45 CFR 46.103.b.5. See also, U.S. Department of Health, Office for Human Research Protections, *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, para. G, Jan. 2007.)

Under the regulations, the terms “department head” and “agency head” refer to federal authorities. The term “appropriate institutional officials” refers to the officials within the university or institution who are designated by the institution’s internal written procedures to receive the information. The regulations further specify that reports to be made to federal “department and agency heads shall also be made to the Office for Human Research Protections”... (45 CFR 46.103.a.)

***United States Regulations: Food and Drug Administration (21 CFR 56.108; 21 CFR 56.113; 21 CFR 312.50; 21 CFR 312.56; 21 CFR 312.64)***

The U.S. Food and Drug Administration (FDA) regulations outline few direct REB or investigator duties to report to regulatory authorities. Typical is an investigator’s duty to report promptly to the sponsor any adverse effect in a clinical trial that may reasonably be regarded as probably caused by the drug (21 CFR 312.64). The regulations also indicate that investigators have a duty to report unanticipated problems to the research ethics committee, and that research ethics committees need to follow written procedures for ensuring prompt reporting to the FDA of “unanticipated problems involving risks to human subjects.” (21 CFR 312.56; 21 CFR 56.108). 21CFR 56.113 further specifies that research ethics committees must promptly report to the FDA their decision to terminate or suspend approval of a study. The sponsor is generally responsible for reporting adverse events to the FDA. (21 CFR 312.50.) See also, FDA (Draft) *Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting – Improving Human Subject Protection* (Apr. 2007).

***Australia: National Statement on Ethical Conduct in Research Involving Humans, 2007 (superseding the 1999 Statement)***

For years, Australia has been the sole jurisdiction, of those surveyed, that imposed a clear and direct duty on researchers to report adverse events to regulatory authorities. As in Canada, Australian federal drug law imposes a reporting duty on sponsors to regulatory authorities (*The Therapeutic Goods Act* and implementing regulations). The regulations further require clinical trials adherence to ICH-GCP and to the Australian National Health and Medical Research Council, *National Statement on Ethical Conduct in Research Involving Humans of 1999*. Until 2007, article 12.8 of the 1999 National Statement had imposed an adverse event reporting requirement on researchers: to report “serious or unexpected adverse events” to the relevant institutional research ethics committee and to regulatory authorities. The recently revised National Statement continues to outline a duty to report adverse events, but no longer specifies a researcher’s duty to report directly to regulatory authorities. *National Statement on Ethical Conduct in Research Involving Humans, 2007*, art. 3.3.22.c.

## II. Points to Consider

In considering the merits of specifying a new TCPS duty, under which REBs and/or investigators would report new information arising from clinical trials to regulatory authorities, some of the following points have emerged:

- Duty to report: what, when, by/to whom?
- Communication lines: sponsor, investigator and REB reporting duties—will amendments clarify, confuse or duplicate reporting?
- Rationale(s) for any duty to report: need clear purpose(s) and effective means
- Regulatory follow-up: how would regulators act on the new information?
- Harmonization: TCPS with non-TCPS norms (e.g., federal law)
- Confidentiality and proprietary information
- REB administration: would a new TCPS duty help or hinder REBs?
- Scope of any such duty: report to Canadian, U.S., European etc., regulators
- Investigator-driven studies: a special case
- TCPS duty versus professional option: professional integrity/conscience.

## III. Basic Points of Discussion

Under existing Canadian law, sponsors of drug studies have the general duty to report adverse events/safety information to regulatory authorities. Researchers or REBs have a duty to do so in some exceptional instances, such as during investigator-initiated research and for emergency use of experimental drugs under Health Canada's Special Access Programme for Drugs. As noted above, under U.S. regulations, institutions and perhaps REBs have an indirect duty to report to regulatory authorities.

Under PRE's Working Committee's recommendations, investigators have a clear duty to share new material information, first with the REB and then with participants. Contracts with restrictive clauses will have been scrutinized as part of the ethics review process. Under the recommendations, the resolution of arguments about the scope of disclosure should be guided by a paramount concern for the safety of participants (commentary to new article 7.5). Duties to participants in clinical trials beyond one's base institution might be considered secondary to the primary duties owed to participants recruited at one's base institution. In this context, imposition of an additional duty to share/report to regulatory authorities would need to be considered in light of the factors in part II (Points to Consider) above. The TCPS should not discourage researchers from sharing information with regulatory authorities if, in their independent and professional ethics judgment, it will avoid harms.

The following table summarizes the reporting duties outlined above. Full references to the policies or regulations are noted in the appropriate sub-section above.

	Reporting to Regulatory Authorities							
	AUST <sup>18</sup>	CAN <sup>19</sup>	CAN <sup>20</sup>	CIOMS <sup>21</sup>	EU <sup>22</sup>	ICH <sup>23</sup>	U.S. <sup>24</sup>	WHO <sup>25</sup>
Serious/unexpected adverse event/reaction, unanticipated problems involving risk	S	S	P		S	S	S, I/E	
Trial suspension/termination		S				U	E	
REB suspension of research		S					I	
Protocol amendments		S			S			
Serious non-compliance				E		S	I	
Monitoring: follow-up								E

Key: S=sponsor I=institution E=ethics committee P=practitioner (e.g., MD) U= unspecified

<sup>18</sup> Australia, *Therapeutic Goods Act 1989* and *National Statement on Ethical Conduct in Research Involving Humans, 1999*.

<sup>19</sup> Canada, *Clinical Trial Regulations*.

<sup>20</sup> Canada, *Special Access Programme-Drugs*.

<sup>21</sup> Council for International Organizations of Medical Sciences.

<sup>22</sup> European Union, *Clinical Trials Directive 2001/20/EC* (2001).

<sup>23</sup> International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use Guidance E6: *Good Clinical Practice: Consolidated Guideline*.

<sup>24</sup> United States, *FDA Regulations* and *Federal Common Rule*.

<sup>25</sup> World Health Organization, *Operational Guidelines*.