
**Recommendations – Researchers’ Continuing Duty to Share
New Information in Clinical Trials;
Confidentiality Clauses in Ethics Review;
Continuing Consent Duties and REB Purpose and Functions**

Submitted by the

**Working Committee on Clinical Trials Information:
a Working Committee of the
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The content and views expressed in this document are those of members of this committee, and do not necessarily reflect those of the Interagency Advisory Panel or Secretariat on Research Ethics.

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Purpose

The following provides recommendations for change to the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS).

Background

In 1993, Dr. Nancy F. Olivieri was working as a hematologist and researcher at the Hospital for Sick Children and professor of medicine at the University of Toronto when she entered into multiyear clinical trial agreements with the pharmaceutical company Apotex Inc. to conduct research on deferiprone, a potential new drug to counteract iron overload in thalassemic¹ patients.

After a couple of years, Dr. Olivieri had concerns about the efficacy and safety of the drug. When she attempted to inform her patients of these possible side effects, she was reminded of the agreements she had signed that indicated that all findings and data were to remain confidential and were the property of Apotex without expressed permission for disclosure, and she was advised any violations would be legally pursued.

A cascade of disputes followed.

In October 2001, the Canadian Association of University Teachers (CAUT) published a report in which a number of recommendations were made. Some recommendations were directed towards the Agencies, in particular to address non-disclosure clauses in contracts and agreements in the TCPS. In May 2003, the Agencies directed the Interagency Advisory Panel on Research Ethics (PRE) through a Presidential Reference (Appendix A) to develop proposals for change in the TCPS. PRE struck the Working Committee.

The Duty to Share Information: A Foundation for the Recommendations

The following recommendations generally address related responsibilities aimed at more explicitly incorporating into the TCPS modern standards that bear on the sharing of new information that arises in clinical trials.

The recommendations are based on a review of the leading Olivieri reports², pertinent national and international documents, and the interdisciplinary literature relevant to the Presidents' Reference.

¹ Thalassemia is a form of anemia which in its severe form requires a patient to undergo repeated blood transfusions. However, blood transfusions can cause excess iron stores in the body, which in turn can be harmful.

² Naimark et al. *Clinical Trials of L1 (Deferiprone) at The Hospital for Sick Children: A Review of Facts and Circumstances*, Dec. 1998 (Naimark Report); Hospital for Sick Children. *Research Policy Review Task Force Report*, Dec. 1999; Thompson, Baird & Downie. *Report of the Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, The Hospital for Sick Children, the University of Toronto, and Apotex Inc.* Canadian Association of University Teachers (CAUT), Oct 2001; *A Commentary by Arnold Naimark, Bartha Knoppers and Frederick Lowy on the CAUT Report*, Dec. 2001 (Naimark Supplement); Thompson, Baird & Downie. *Supplement to the Report of the Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto, and Apotex Inc.* CAUT, Jan. 2002. (Thompson et al. Supplement).

Consistent with the Presidents' Reference, the Committee gave priority attention to Recommendations 1 and 25 of the CAUT Olivieri Report but looked at and addressed others as well (Appendix B). The Committee agrees with the general tenor of the CAUT recommendations. It finds that they address an ethical issue central to most of the reports that the Olivieri saga has inspired: namely, the researcher's timely sharing of new information that arises in the clinical trial process.

The Olivieri incident raises a general question: Does/should an investigator have a duty to share new information that arises in the course of a clinical trial, with trial participants, REBs or related entities? Whether it is grounded on a paramount concern for patient safety, autonomy, informed consent, and associated principles of doing no harm, or a researcher's fiduciary duty, most reports and much of the literature agree that investigators have a duty to share new risk information on a timely basis. The Committee shares this view.

Technical dialogue and targeted public consultations on the draft working recommendations generally revealed strong support for their general direction and underlying principles. They underscored some ambiguities, questions and sub-issues. As a result, the recommendations have benefited from clarification and strengthening. Most issues raised in the technical and targeted consultations have been incorporated into the recommendations. A summary of some leading clarifications, revisions or issues follows. The numbers refer to line items in the recommendations below.

- ✓ 1. Contract Review: Indicate that if a university contract research officer reviews clinical trial contracts and channels the results to the REB, he/she does so with the special ethics duties of the REB. **(Lines 35-39)**
- ✓ 2. Suppression: Endorse a multi-faceted approach to non-suppression of data.
- ✓ 3. Researcher/REB Conflict: What happens if a researcher and an REB disagree over the need to share new information with participants in the clinical trial? Response: Incorporate reference to REB appeals, and insert a precautionary principle to guide conflicted decision-making. **(Lines 76-80)**
- ✓ 4. Reporting to Regulatory Authorities: Should the TCPS impose a new researcher and/or REB duty to report adverse events to regulatory authorities? The recommendations include two options to address this in a new article. **(Lines 89-115)**
- ✓ 5. DSMBs: Recognize the role of independent data safety monitoring boards (DSMB) in the objective interpretation and monitoring of new information. **(Lines 158-159)**
- ✓ 6. Harms: Summarize the harms that may flow from suppression of research results. **(Lines 168-173)**
- ✓ 7. What length of time should be indicated as a reasonable period of delay for sponsors' review of data, publications drafts or patent issues for university policies? Response: Amend the example of a reasonable period of delay from 6-12 months in the initial draft to 3-6 months in the revised draft. The amendment is based on new institutional policies in Canada, persuasive trends and harmonization with policies in the United States, and the literature, as noted in Appendix C below. **(Lines 179-187)**

- ✓ 8. Consent: Amend art. 2.4 of the TCPS on informed consent to include a researcher's duty to disclose measures to be taken to publish and disseminate research results. (**Lines 251-252, 267-271**)
- ✓ 9. Conflict of Interest: Beyond amending article 7.3, the Committee agrees that the TCPS should give further explicit direction to REBs and institutions to identify and manage conflicts of interests. Accordingly, the Working Committee urges, as a matter of priority, the PRE to undertake a review and update of chapter 4 of the TCPS to address modern conflict of interest (COI) matters.
- ✓ 10. Purpose of REB Review: In underlining the role of REBs in protecting participants' rights, safety and welfare, clarify that the protective function arises in a diversity of research contexts, ranging from biomedical to critical social science research. (**Lines 307-308, 315-321**)
- ✓ 11. Broader Research Suppression: Recommendation: The dissemination of research data and/or results should be recognized as an important university issue beyond clinical trials.
- ✓ 12. Health Canada Recommendation: Health Canada norms regarding a researcher's duty to share information with the REB would benefit from clarification.
- ✓ 13. Adverse Events: PRE should signal the need for urgent action to address the flood of paperwork and uncertainty surrounding adverse events reports to REBs.
- ✓ 14. Ethical Principle of Dissemination of Research Results: The Committee has proposed text to include this principle in the TCPS Ethics Framework. (**Lines 383-385, 390**)

Overview of Recommendations

The Committee debated whether the TCPS should specify an investigator's duty to share timely information that arises in a clinical trial. As Appendix C indicates, the existing TCPS does refer to an investigator's responsibilities to share information as part of continuing consent and clinical trials duties. However, it may not provide optimal guidance, because it sketches responsibilities without clarity and specificity. Indeed, the Committee finds that the TCPS lacks the kind of explicit standard and specificity of the 1987 Guidelines of the former Medical Research Council of Canada, and lacks the precision and details found in other leading national and international documents.

To respond to these limitations and recommendations 1 and 25 of the CAUT Report, the Committee proposes recommendations for four related sections of the TCPS. The working recommendations are intended to clarify the investigator's duty to share timely information in clinical trials, by clarifying the investigator's continuing consent duties, by specifying the REB role in reviewing contracts that unduly restrict the sharing of information, and by clarifying one of the REB's basic functions in initial and ongoing ethics review of clinical trials.

- Section 7: *Clinical Trials*: To make explicit a researcher's ongoing duty to share new risk/benefit information from the clinical trial process with REBs and/or participants on a timely basis. The urgency of the timing should be proportionate to the potential seriousness of the risk raised by the information.

- Section 7: *Clinical Trials*: To make explicit the need to review confidentiality clauses in contracts between investigators and industry, as part of research ethics review, and to do so on the basis of reasonable written institutional policies about such clauses and publication bans.
- Section 2: *Informed Consent*: To make explicit a researcher's continuing consent duties and participants' reasonable expectations that research results will normally be published or otherwise publicly disseminated.
- Section 1: *REB Purpose, Review and Ongoing Review*: To make more precise the REB's purpose and its duties to manage new information as part of ethics review, and to make these duties an explicit part of ongoing REB review.
- *Ethical Framework*: To make explicit reference to the principle of public dissemination of the results of research, as part of the values of science, scholarship and accountability to participants, peers and society.

The bulk of the proposed amendments focus on the Clinical Trials section of the TCPS with complementary amendments to the Free and Informed Consent and Ethics Review sections.

1 RECOMMENDATIONS FOR SECTION 7: CLINICAL TRIALS

2
3 **Nota:** Underlined Text = New Recommended Text;

- 4
5 A. Clinical Equipoise
6 B. Phases of Pharmaceutical Research
7 C. Budgets, Contracts and Agreements
8 D. Multicentre Clinical Trials
9 E. Placebo-Controlled Studies
10 F. Sharing New Information
11 G. Analysis and Dissemination of the Data and Results of Clinical Trials
-

13 14 C. Budgets, Contracts and Agreements

15 16 Article 7.3

17
18 **REBs shall ensure that budgets, contracts and investigator agreements regarding clinical trials are**
19 **properly examined to assure that ethical duties concerning conflict of interest are respected.**
20

21 Budgets for clinical trials are usually calculated on per capita costs, that is, the sponsor pays the
22 researcher a fixed sum for each research subject recruited, based on the length of time that the subject is
23 on the study and the tests required by the trial. Unreasonable payments or undue inducements raise ethical
24 concerns because of the potential to place the researcher in a conflict between maximizing economic
25 remuneration and serving the best health interests of subject-patients, especially if the researcher also
26 holds a therapeutic or clinical or other fiduciary relationship with the subjects. Disclosure of the kinds and
27 amounts of the payments, and other budgetary details, will assist the REB, or other delegated body within
28 the institution, to assess potential conflicts of interest, and may also assist the researcher in resolving
29 them. As a general guide, payments should be comparable to the physician's or researcher's usual
30 professional fee for the provision of comparable services. When trials take place within a public
31 institution, such as a hospital or a long-term care facility, recovery of utilization costs for institutional and
32 other resources (such as radiological and diagnostic services) should be considered essential, and should
33 be in addition to any overhead charge stipulated by the institution.
34

35 The independent review of the investigator-industry contract should be undertaken by a duly composed
36 REB, or by or under the auspices of another competent institutional authority that shares the results with
37 the REB, as an integral part of the ethics review process. If done under the latter process, the review of
38 contracts should be conducted (i) in a manner that conforms to the special ethical duties, mandate and
39 purposes of REB review, and (ii) in consultation with the REB when necessary.
40

41 **F. Sharing New Information**

42 **Article 7.5**

43
44 **(a) If, in the course of a trial, new information arises that may be relevant to participants' free,**
45 **informed and continuing consent to participation in the research, investigators should share the**
46 **information, in a timely manner, with the REB and participants. The urgency of the timing should**
47 **be commensurate with the potential seriousness of the risk raised by the information. In some**
48 **circumstances, new information that arises after a trial may also need to be shared.**
49

50 Article 7.5 outlines an investigator's continuing duty to share new and relevant information from the
51 clinical trial process with the REB and research participants. "New information" is information that may

52 affect the willingness of a participant to continue in the trial, or that is otherwise relevant to participants’
53 free, informed, and continuing consent. (See articles 2.1, 2.4.f) To understand its particular relevance, the
54 information needs to be considered from a participant-centered perspective. This sharing may also include
55 new information that arises outside the trial when that information is relevant to the participant’s
56 informed and continuing participation. “New information” thus covers a range of matters that includes,
57 but is not limited to, the following:

- 58
- 59 - changes to the research protocol;
- 60 - new risk information, such as adverse events or safety data;
- 61 - new information which shows benefits of one intervention over another;
- 62 - new findings, including important non-trial information;
- 63 - unanticipated problems involving therapeutic efficacy or recruitment issues.
- 64

65 Duties to report such new information to the REB lies with the sponsor and the investigator. The REB’s
66 interdisciplinary advice should help structure the breadth and timing of sharing the information with
67 participants. The more serious and urgent the information, the more promptly it should be shared.

68

69 In those circumstances when significant risk/benefit information arises after the trial, and which may well
70 affect the well-being or safety of former participants, the investigator should share the information with
71 the REB. The REB and investigator should consider whether, given the nature and urgency of the
72 information, a reasonable former participant would, under the circumstances, consider the information
73 relevant to his or her well-being and informed choices. If so, then reasonable steps should be taken to
74 share the information in a meaningful and timely manner with former participants.

75

76 In the event that a researcher and REB were to disagree over the sharing of new information with
77 participants, attempts to resolve the disagreement should involve recourse to the REB appeals process
78 (see articles 1.10-1.11, above). The REB process should be cognizant of, and sensitive to, the urgency of
79 the matter. Attempts to resolve disagreement about the scope and reach of disclosure should be guided by
80 a paramount principle of protecting the safety and welfare of trial participants.

81

82 **(b)**

83 *Nota: This proposed sub-article 7.5(b) outlines two options regarding a TCPS duty to share new clinical*
84 *trial information with regulatory authorities. Both options address researcher and sponsor disagreement*
85 *over reporting the new information to relevant regulatory authorities. Option A recognizes that the duty*
86 *may arise, as a matter of professional conscience, given a number of factors. Option B outlines a special*
87 *duty to report the information when a sponsor refuses to do so.*

88

89 **Option A (Good Conscience Clause): In exceptional instances of intractable disagreement, where all**
90 **other reasonable measures have been exhausted, the principle of protecting the safety and welfare**
91 **of patients should further guide researchers and REBs about the lengths to which they should go to**
92 **share new, relevant and important information. If, in good conscience, a researcher or REB,**
93 **exercising independent and professional judgment, were to determine that sharing information**
94 **likely would prevent significant harms to research participants, then the researcher or REB may**
95 **reasonably conclude that there is an ethical duty to do so, despite objections. The scope of the**
96 **duty—what new information should be disclosed, when it should be disclosed, and to whom it**
97 **should be disclosed—should be proportionate to the seriousness and urgency of the potential harm.**

98

99 Option A addresses exceptional circumstances that might arise, for example, if a research sponsor were to
100 refuse to report to regulatory authorities new and significant information. In such circumstances, should
101 the researcher or REB report the new information to regulatory authorities? In their deliberations on such
102 matters, researchers and REBs should consider such factors as: whether the information is novel and
103 significant or duplicative; the objective quality and nature of the information; the direct relevance of the
104 information to participants’ safety, welfare and continuing consent; whether relevant entities (sponsors,

105 data safety monitoring boards, and REBs) have been afforded a reasonable opportunity to discharge their
106 duties with respect to the information, and relevant regulatory duties.

107
108 **Option B (Special Duty to Report to Regulatory Authorities): In exceptional circumstances, beyond**
109 **those required under existing regulations, the ethical principles of avoiding harm and respecting**
110 **participants' informed consent impose on researchers or REBs a special duty to share new safety-**
111 **efficacy information with regulatory authorities. When sponsors refuse to report new and**
112 **significant information that is relevant to the safety and welfare of participants, then researchers**
113 **and/or REBs have a duty to do so. The more objectively relevant and urgent the information, the**
114 **stronger the duty. Before REBs or researchers act on such duties, they should afford sponsors a**
115 **reasonable opportunity to report the information to the appropriate regulatory authorities.**

116 117 **G. Analysis and Dissemination of the Data and Results of Clinical Trials**

118 119 **Article 7.6**

120
121 **(a) Institutions and REBs should develop reasonable written policies regarding confidentiality**
122 **clauses and publication clauses in research contracts between investigators and industry.**

123
124 A reasonable institutional policy should:

- 125
126 i. require that confidentiality and publication clauses be submitted to the responsible authority (e.g.
127 REB, research administration) for a determination of their adherence to the written policy of the
128 institution;
129
130 ii. require that the results of the review be shared with the REB as an integral part of the ethics review
131 process.
132
133 iii. provide that all confidentiality and publication clauses:
134
 - 135 ▪ be consistent with the investigator's duty to share new information from the clinical trial setting
136 with REBs and trial participants in a timely manner, under articles 7.5 and 2.1(a);
 - 137 ▪ be reasonable in terms of any limitations or restrictions on the dissemination or communication of
138 information;
 - 139 ▪ address data sharing/ownership; and
 - 140 ▪ address publication rights and authorship of the initial and subsequent reports in multicentre
141 trials.

142 **(b) Absolute bans on the dissemination of scientific information from clinical trials are ethically**
143 **unacceptable. Confidentiality clauses or publication limitations that impose unduly broad**
144 **limitations on either the content of the scientific information that may be disseminated or on the**
145 **timing of that dissemination are presumed to be ethically unacceptable.**

146
147 In many clinical trials, the sponsors have contractual rights to the initial analysis and interpretation of the
148 resultant data. These provisions are typically found in industry-investigator contracts³ that may not
149 always be part of an REB review. To incorporate the analysis of these contractual provisions into modern
150 interdisciplinary ethics review, articles 7.6(b) and 7.3 require (a) that institutions and REBs adopt

³ Steinbrook R. Gag Clauses in Clinical-Trial Agreements. *NEJM*, 2005;352:2160-62; Mello MM, Clarridge BR, Studdert DM. Academic Medical Centers' Standards for Clinical Trial Agreements with Industry, *NEJM*, 2005; 352:2202-10. Schulman KA, Seils DM, Timbie JW et al. A National Survey of Provisions in Clinical-Trial Agreements between Medical Schools and Industry Sponsors. *NEJM*, 2002; 347:1371-1375. Editorial. The Controlling Interests of Research. *CMAJ* 2002; 167 (11).

151 reasonable written policies regarding such provisions; and (b) that contracts and relevant documents for
152 proposed research be independently reviewed for their consistency with these policies and principles.
153
154 Article 7.6 is intended to ensure that any such contractual rights be reasonably balanced against the
155 investigator's ethical and legal obligations to participants in trials and the scientific and public good in the
156 dissemination of the data and results of research. For example, where stopping rules are in place,
157 monitoring of the interim results must be done independently, for example, by an independent data safety
158 monitoring board (DSMB). Properly composed and duly accountable DSMBs play an important role in
159 ensuring independent overall analysis of clinical trial data and complement the role of the REB.⁴ It should
160 also be remembered that, with a stopping rule in place, long-term positive or negative effects might be
161 masked by short-term harms or benefits.
162
163 Measures necessary for the effective discharge of the duties of researchers and institutions to share new
164 information and disseminate the analysis and interpretation of their results to the research community may
165 need to be undertaken. Based on the principles of scientific process, respect for participant expectations
166 and the protection of the public good, research scientists and institutions have an ethical responsibility to
167 make reasonable efforts to disseminate publicly the results of research in a timely manner.⁵
168 Unfortunately, however, negative results and outcomes of research frequently are not published or
169 disseminated. Silence on such results may lead to data suppression and publication bias⁶ and thus
170 contribute to a series of harms: misinformed decision-making based on a mis-weighting of risks and
171 benefits, inappropriate and potentially harmful clinical practices and injury to health, needless and
172 wasteful duplication of research interventions on participants, fraud or deception in the clinical trials
173 process and erosion of public trust and accountability in research. Research journalists, journal editors,
174 members of editorial peer review boards, sponsors and regulators should continue to address this as an
175 issue of scientific and ethical urgency. Clinical trials registries,⁷ editorial policies,⁸ ethical policy reforms,
176 and revised national and institutional ethics policies all contribute to a multi-faceted approach to
177 combating the ills of non-disclosure and the suppression of data in clinical research.
178
179 In the review process, the onus to justify significant restrictions on dissemination should lie on the
180 researcher and, when appropriate, the sponsor. The reasonableness of the restrictions on either the content
181 or timing of dissemination should be measured against the standards of the written institutional policies.
182 For example, some existing university policies deem publication restrictions that exceed a reasonable time
183 limit, e.g., 3-6 months after the close of the trial, to be unacceptable. Such written institutional policies
184 should also address restrictions on the dissemination of particular kinds of information, such as
185 information that may be considered proprietary/trade secret and information that participants would
186 reasonably consider relevant to their welfare or safety. Consistent with Articles 2.1 and 7.5, restrictions
187 on the latter are seldom, if ever, justified.
188

⁴ Council of International Organizations of Medical Sciences (CIOMS), *Management of Safety Information from Clinical Trials: Report of CIOMS Working Group VI*. CIOMS: Geneva, 2005; 265-27; Slutsky AS, Lavery JV. Data Safety and Monitoring Boards. *NEJM*, 2004; 350 (11):1143-7.

⁵ See article 2.4f, and accompanying commentary, above. Accord: *Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*, 2005, art. 28.

⁶ See, e.g., Chan AW, Krleza-Jeric K, Schmid I et al. Outcome Reporting Bias in Randomized Trials Funded by the Canadian Institutes of Health Research. *CMAJ*, 2004; 171(7):735-740.

⁷ See, e.g., International Committee of Medical Journal Editors, Is this Clinical Trial Fully Registered? — A Statement from the International Committee of Medical Journal Editors, *NEJM*, 2005; 362:2436-2439; Krleza-Jeric K, Chan AW, Dickersin K, Sim I et al. Principles for International Registration of Protocol Information and Results from Human Trials of Health Related Interventions: Ottawa Statement (Part I). *BMJ* 2005; 330:956-958. Moher D, Bernstein A. Registering CIHR-funded Randomized Controlled Trials: A Global Public Good. *CMAJ*, 2004; 171:750-751; European Union, *Clinical Trials Directive, 2001*, art. 11; www.clinicaltrials.gov.

⁸ International Committee of Medical Journal Editors (ICMJE), *Statement on Conflicts of Interest, 2001*.

189 **RECOMMENDATIONS FOR SECTION 2: FREE AND INFORMED CONSENT**

190
191 *Nota: To complement the working recommendations on clinical trials, the underlined text, below,*
192 *proposes clarifying and bringing technical amendments to the Free and Informed Consent section of the*
193 *TCPS. They are intended to make explicit what is implied and dispersed throughout the existing articles*
194 *and commentary: namely, a researcher's ongoing duty throughout the research project to share*
195 *information relevant to a participant's informed participation in the research. The amendments would*
196 *affect the title, add a new clause to article 2.4, and insert new text in articles (2.1 and 2.4) of the section.*
197

198 **A. Requirement for Free, Informed and Continuing Consent**

199
200 **Article 2.1**

201
202 **Free and informed consent encompasses a process that begins with a researcher's initial contact**
203 **with participants and that continues through to the end and sometimes beyond the research**
204 **project. Throughout the process, researchers have a continuing duty to provide participants and**
205 **REBs information relevant to the participant's free and informed consent to participate in the**
206 **research.**

207
208 **(a) Research governed by this Policy (see Article 1.1) may begin only if:**

209 **(1) prospective subjects, or authorized third parties, have been given the opportunity to give**
210 **free and informed consent about participation, and**

211 **(2) their free and informed consent has been given and is maintained throughout their**
212 **participation in the research. Articles 2.1(c), 2.3 and 2.8 provide exceptions to Article 2.1(a).**

213
214 **(b) Evidence of free and informed consent...**

215
216 As used in this Policy, the process of free and informed consent refers to the dialogue, information
217 sharing and general process through which prospective subjects choose to participate in research
218 involving themselves.

219
220 Article 2.1(a) states the requirement in both ethics and law: to protect and promote human dignity. Ethical
221 research involving humans requires free and informed consent. As elaborated more fully below, free and
222 informed consent is exercised by an authorized third party for those who lack legal competence. ...

223
224 **Article 2.4**

225
226 **Researchers shall provide, to prospective subjects or authorized third parties, full and frank**
227 **disclosure of all information relevant to free and informed consent. As part of a researcher's**
228 **continuing duties throughout the free and informed consent process, the researcher must ensure**
229 **that prospective subjects are given adequate opportunities to discuss and contemplate their**
230 **participation. Subject to the exception in Article 2.1(c), at the commencement of the free and**
231 **informed consent process, researchers or their qualified designated representatives shall provide**
232 **prospective subjects with the following:**

233
234 **(a) Information that the individual is being invited to participate in a research project;**

235
236 **(b) A comprehensible statement of the research purpose, the identity of the researcher, the**
237 **expected duration and nature of participation, and a description of research procedures;**

238
239 **(c) A comprehensible description of reasonably foreseeable harms and benefits that may arise from**
240 **research participation, as well as the likely consequences of non-action, particularly in research**

241 related to treatment, or where invasive methodologies are involved, or where there is a
242 potential for physical or psychological harm;

- 243
- 244 (d) An assurance that prospective subjects are free not to participate, have the right to withdraw at
245 any time without prejudice to pre-existing entitlements, and will be given continuing and
246 meaningful opportunities for deciding whether or not to continue to participate; and
247
- 248 (e) The possibility of commercialization of research findings, and the presence of any apparent or
249 actual or potential conflict of interest on the part of researchers, their institutions or sponsors.
250
- 251 (f) The measures to be undertaken to publish or otherwise make publicly available the results of
252 the research.
253

254 *Excerpts from Existing Commentary to Article 2.4*
255

256 Under the normal process of obtaining written consent, the prospective subject should be given a copy of
257 the consent form and any relevant written information. The consent of the participants shall not be
258 conditional upon, or include any statement to the effect that, by consenting, subjects waive any legal
259 rights.
260

261 In light of (b) and (c), REBs may require researchers to provide prospective subjects with additional
262 information, such as that detailed in Table 1 below.
263

264 ...Article 2.4(d) also requires that researchers specifically ascertain continuing consent from subjects on
265 the basis of new information.
266

267 Article 2.4(f) requires that researchers provide a reasonable explanation of the measures to be undertaken
268 to publish and otherwise disseminate the results of the research. Beyond the ethical obligation to do so in
269 such areas as clinical trials (see articles 7.6(a) and 7.6(b) below), this requirement is grounded on the
270 reasonable expectation of participants in research that the results will be published or otherwise
271 disseminated in the public domain to advance societal knowledge.
272

273 **Table 1: Additional information that may be required for some projects**
274

- 275 1. An assurance that new information will be provided to the subjects in a timely manner whenever such
276 information is relevant to a subject's decision to continue or withdraw from participation;
- 277 2. The identity of the qualified designated representative who can explain scientific or scholarly aspects
278 of the research;
- 279 3. Information on the appropriate resources outside the research team to contact regarding possible
280 ethical issues in the research;
- 281 4. An indication as to who will have access to information collected on the identity of subjects,
282 descriptions of how confidentiality will be protected, and anticipated uses of data;
- 283 5. An explanation of the responsibilities of the subject;
- 284 6. Information on the circumstances under which the researcher may terminate the subject's
285 participation in the research;
- 286 7. Information on any costs, payments, reimbursement for expenses or compensation for injury;
- 287 8. In the case of randomized trials, the probability of assignment to each option;
- 288 9. For research on biomedical procedures, including health care interventions: information about (a)
289 foregoing alternative procedures that might be advantageous to the subject, (b) which aspects of the

290 research involve the use of procedures that are not generally recognized or accepted; and (c)
291 particularly in trials of therapeutic interventions, the care provided if the potential subject decides not
292 to consent to participation in the study;

293 10. How the subjects will be informed of the results of the research.

294

295 **RECOMMENDATIONS FOR SECTION 1: ETHICS REVIEW**

296

297 *Nota: The underlined language below recommends amendments to clarify and make explicit the*
298 *fundamental purpose and function of REB review. The amendment would address Olivieri matters, and*
299 *harmonize the TCPS with leading international standards. It is also recommended that researchers'*
300 *continuing consent and information sharing duties be cross-referenced with the REB's duties concerning*
301 *ongoing review (art. 1.13).*

302

303 **B1. Purpose and Authority of the REB**

304

305 **Article 1.2**

306

307 **(a) The primary purpose of REB review is to protect the dignity, well-being, rights and safety of**
308 **research participants.**

309

310 **(b) The institution in which research involving human subjects is carried out shall mandate the**
311 **REB to approve, reject, propose modifications to, or terminate any proposed or ongoing research**
312 **involving human subjects which is conducted within, or by members of, the institution, using the**
313 **considerations set forth in this Policy as the minimum standard.**

314

315 Article 1.2(a) indicates the primary purpose of human research ethics review. Respecting the dignity and
316 protecting the rights of participants reflect fundamental values in research ethics. Those values will
317 sometimes conflict with others, such as the societal good that may derive from research. The value
318 conflict is endemic in REB review, as recognized in the ethics framework of the TCPS. Under the
319 framework, the functions of REB review need to be exercised and applied thoughtfully to diverse research
320 contexts. Those contexts range from the safety risks posed by health science research to critical social
321 sciences research the purpose of which is to critique those under study.

322

323 **F. Review Procedures for Ongoing Research**

324

325 **Article 1.13**

326 **(a) Ongoing research shall be subject to continuing ethics review. The rigour of the review should**
327 **be in accordance with a proportionate approach to ethics assessment.**

328 **(b) As part of each research proposal submitted for REB review, the researcher shall propose to**
329 **the REB the continuing review process deemed appropriate for that project.**

330 **(c) Normally, continuing review should consist of at least the submission of a succinct annual status**
331 **report to the REB. The REB shall be promptly notified when the project concludes.**

332 As part of continuing ethics review, researchers should fulfill their responsibilities for continuing consent
333 and the reporting of new information that arises in clinical trials, consistent with Articles 2.1 and 7.5.

334

335 Beyond scrutinizing reports, the REB itself should not normally carry out the continuing ethics review,
336 except in specific cases where the REB believes that it is best suited to intervene. For research posing
337 significant risks, the REB should receive reports on the progress of the project at intervals to be

338 predetermined. These reports should include an assessment of how closely the researcher and the research
339 team have complied with the ethical safeguards initially proposed.

340

341 In accordance with the principle of proportionate review, research that exposes subjects to minimal risk or
342 less requires only a minimal review process. The continuing review of research exceeding the threshold of
343 minimal risk that is referred to in Article 1.13 (b), in addition to the annual review (Article 1.13 (c)) might
344 include:

- 345 • a formal review of the free and informed consent process,
- 346 • the establishment of a safety monitoring committee,
- 347 • a periodic review by a third party of the documents generated by the study,
- 348 • a review of reports of adverse events,
- 349 • a review of patients' charts, or
- 350 • a random audit of the free and informed consent process.

351

352 Other models of continuing ethics review may be designed by researchers and REBs to fit particular
353 circumstances.

354

355 The process of a continuing ethics review should be understood as a collective responsibility, to be
356 carried out with a common interest in maintaining the highest ethical and scientific standards. Research
357 institutions should strive to educate researchers on the process of continuing ethics review through
358 workshops, seminars and other educational opportunities.

359

360 **Recommendations for the TCPS Ethics Framework: Ethical Responsibilities and the Dissemination** 361 **of Research Results**

362

363 *Nota: To complement the proposed amendments to article 2.4(f) and existing references in the*
364 *commentary to article 7.6(a), regarding an ethical responsibility to make publicly available the results of*
365 *research in a timely manner, an amendment is offered for an addition to the TCPS Ethics Framework.*
366 *The amendment proposes to incorporate reference to the ethical principle of dissemination of the results*
367 *of research, as part of the public values of science, scholarship and accountability. (See also the*
368 *Committee's commentary following the proposed textual insert).*

369

370 **TCPS ETHICS FRAMEWORK**

371

372 **Academic Freedoms and Responsibilities**

373 Researchers enjoy, and should continue to enjoy, important freedoms and privileges. To secure the
374 maximum benefits from research, society needs to ensure that researchers have certain freedoms. It is for
375 this reason that researchers and their academic institutions uphold the principles of academic freedom and
376 the independence of the higher education research community. These freedoms include freedom of
377 inquiry and the right to disseminate the results thereof, freedom to challenge conventional thought,
378 freedom from institutional censorship, and the privilege of conducting research on human subjects with
379 public monies, trust and support. However, researchers and institutions also recognize that with freedom
380 comes responsibility, including the responsibility to ensure that research involving human subjects meets
381 high scientific and ethical standards. The commitment of researchers and institutions to the advancement
382 of knowledge through scientific and scholarly inquiry entails duties of honest and thoughtful inquiry,
383 rigorous analysis and accountability to participants, peers and society. That broad accountability includes
384 a responsibility to make reasonable efforts to disseminate or otherwise make publicly available the results
385 of research, in a manner respectful of disciplinary and cultural contexts.

386

387 Peer review of research proposals, research findings and their interpretation contribute to accountability,
388 both to colleagues and to society. Review of the ethics of research helps ensure a more general
389 accountability to society. Accountability, moreover, requires that the whole process should always be
390 open to critical assessment and scientific and public debate.

**Reference from the Granting Agencies to the
Interagency Panel on Research Ethics:
TCPS Research Ethics Matters Raised by the Olivieri Report**

The Presidents of the CIHR, NSERC, and SSHRC,

Recognizing

- That recent developments and reports in Canada have given prominent international attention to a range of issues raised by constraints on the non-disclosure of risk information to participants in clinical trials and human research;

- That this and related issues have been discussed in particular in Recommendations 1 and 25 of the *Report of the Committee of Inquiry on the Case Involving Dr Nancy Olivieri, the Hospital for Sick Children, the University of Toronto and Apotex Inc.* (CAUT Olivieri Rpt., 2001) and other important public reports, whose contents and recommendations have been brought to the attention of the Granting Agencies;

- That the issues identified in these reports implicate the national research ethics interest by raising significant policy issues for the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS);

- That such policy issues specifically implicate TCPS standards and procedures concerning, amongst other issues, the informed consent of participants; conflicts of interest; the conduct of clinical trials; researchers' ethical duties; and the continuing monitoring duties of REBs and institutions;

- That the broad research ethics community which uses the TCPS may benefit from further clarity, precision, and guidance on these issues and developments;

- That the independent reflection and advice of pluralistic, interdisciplinary ethics entities may prove instrumental in developing such guidance;

- That the Granting Agencies have recently created the Interagency Advisory Panel on Research Ethics (PRE) to serve such a role, and have delegated to PRE the responsibility to articulate recommendations for the further development and evolution of the TCPS;
-

Therefore, Request the Interagency Advisory Panel on Research Ethics to:

- *Review* (a) the recommendations 1 and 25 of the Olivieri report, as they relate to the disclosure of risk information in clinical trials, (b) other directly relevant recommendations and analyses contained in this and other reports and literature; and (c) pertinent international and national developments and institutional policies, in light of the need to keep the TCPS current with modern research ethics needs; and
- *Consult* with appropriate experts, interests, and stakeholders, including the public; and
- *Report and Advise*, in a timely manner to the Presidents of the three Agencies, on whether, when and how to incorporate proposed recommendations for amendment of the TCPS.

Ottawa, _____ May 2003.

Dr Alan Bernstein
President, Canadian Institutes of Health Research

Dr Tom Brzustowski
President, Natural Sciences and Engineering Research Council of Canada

Dr Marc Renaud
President, Social Sciences and Humanities Research Council of Canada

CAUT Report: Relevant Recommendations (1, 10-14, 25, 26)**General**

1 All contracts, protocols and investigator agreements for industrial sponsorship of clinical trials should expressly provide that the clinical investigators shall not be prevented by the sponsor (or anyone) from informing participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community, of risks to participants that the investigators identify during the research. The same provisions should apply to any risks of a treatment identified following the conclusion of a trial in the event there are patients being administered the treatment in a non-trial setting.

Certain circumscribed confidentiality restrictions may be appropriate, for example, those pertaining to information on the chemical structure, or synthesis of a drug, or its method of encapsulation. However, restrictions on disclosure of risks to patients are not appropriate, subject only to the condition that the investigator believes there is a reasonable basis for identification of the risk. Under the term “risk” we include inefficacy of the treatment, as well as direct safety concerns.

Research Ethics Boards

10 Not only all protocols but also all associated research contracts and investigator agreements should be reviewed and approved by Research Ethics Boards (REBs) to ensure, among other things, that they comply with recommendation 1.

The REBs should ensure that the wording of protocols is congruent with their associated contracts and investigator agreements. REBs should have, and should exercise, the power to withhold approval of any proposed study if any of the associated protocols, contracts and investigator agreements contain inappropriate confidentiality clauses. REBs should be permitted to delegate the authority to conduct reviews of contracts and investigator agreements to the institutional office of research services. However, such delegation should only be done if:

- a) the office is given clear instructions that contracts and investigator agreements must comply with recommendation 1, with the protocols approved by the REB, the ethical standards articulated in the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)* and other norms of research ethics; and
- b) there is an annual process of auditing by the REB of a representative sample of contracts and investigator agreements to ensure consistency between the protocols (and ethical standards) and the contracts and investigator agreements.

11 REBs should ensure that the guidelines in recommendation 10 are understood and followed by all sponsors and investigators. Insertion of the following text in the relevant documents is recommended:

a) *Consent form*

Throughout the research process, you will be given any new information that might affect your decision to participate in the research. In particular, you will be told of any unforeseen risks that may be identified.

b) Protocol

No agreements or contracts between researchers and sponsors that limit the right and the responsibility of the researchers to disclose relevant information about unforeseen risks that becomes known in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community, have been or will be entered into by the researchers.

c) Investigator agreements / contracts

If I have concerns about the safety and/or efficacy of the study drug, X, I have the right and the responsibility to disclose relevant information that becomes known to me in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community.

12 REBs should review project budgets as well as the research protocols and associated contracts and agreements, in order to ensure that all actual and potential conflicts of interests are managed in an ethical fashion.

13 REBs should ensure that protocols and related contracts and agreements make express provision for the management of patient care in the event of premature termination of a research trial, and should withhold approval of the study until such provision has clearly been made.

14 REBs should review institutional policies and practices with respect to access to patient records for research purposes to ensure that they are in compliance with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)*.

Granting Councils

25 In order to help ensure consistency in standards across the country, the Canadian Institutes for Health Research (CIHR), together with the Social Sciences and Humanities Research Council (SSHRC) and the Natural Sciences and Engineering Research Council (NSERC), should impose a requirement that universities and health care institutions receiving any funding from the granting councils have in place the policy in recommendation 1. The requirement should apply to all clinical research projects conducted at these institutions, whether or not such projects are funded by one of the granting councils. A means of ensuring compliance would be the withholding of all CIHR, SSHRC and NSERC funds where such a requirement is not in place, or is not met, and the Councils should actively monitor compliance.

26 The *TCPS* should be amended so as to give further explicit and prescriptive direction to REBs on the need and ways to identify and manage conflicts of interest.

**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
CANADA: TCPS⁹	<ul style="list-style-type: none"> - Participants to be given “continuing and meaningful opportunities for deciding whether... to continue to participate.” - “New information” for informed participation - Monitoring “unexpected adverse events” 	<ul style="list-style-type: none"> - Ongoing - Ongoing (implied) - Not specified, but presumably ongoing 	<ul style="list-style-type: none"> - To participants, by the researcher - To participants, by the researcher - To the REB, by the investigator 	<ul style="list-style-type: none"> - Informed consent, art. 2.4(d) - Continuing consent commentary, art. 2.4, p. 2.6 - Clinical trials commentary, art.7.1, p. 7.4
CANADA: MRC ‘87¹⁰	“Apparent risks” beyond those predicted	Immediately	To the REB, by the investigator	Researcher’s “accountability”
CANADA: Clinical Trial Regulations¹¹	“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
CIOMS¹²	<ul style="list-style-type: none"> - “Material changes”; new information – from the study or other sources – about risks and benefits. (Guideline 4) - “Significant changes” in conditions or procedures, or new information that could affect willingness to participate. 	Promptly (Guideline 4)	<ul style="list-style-type: none"> - To participants, by investigators (Guideline 4); - To REBs (Guideline 4), by sponsors, if results not to be disclosed to subjects and investigators - To data safety monitoring board, by investigators 	Consent, initial and continuing

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

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

¹¹ Canada. *Food and Drug Regulations*, Part C, Division 5, s. C.05.014.

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

	WHAT	WHEN	TO WHOM / BY WHOM	BASIS
European Union¹³	- 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”
ICH¹⁴	- 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
U.S. FDA¹⁵	- 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
U.S. HHS¹⁶	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
HELSINKI¹⁷	“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

¹³ 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.*

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

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

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

¹⁷ World Medical Association, *Declaration of Helsinki* (2000), guideline 13.

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:

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 ¹⁸	CAN ¹⁹	CAN ²⁰	CIOMS ²¹	EU ²²	ICH ²³	U.S. ²⁴	WHO ²⁵
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

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

¹⁹ Canada, *Clinical Trial Regulations*.

²⁰ Canada, *Special Access Programme-Drugs*.

²¹ Council for International Organizations of Medical Sciences.

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

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

²⁴ United States, *FDA Regulations and Federal Common Rule*.

²⁵ World Health Organization, *Operational Guidelines*.

Recommendations on Unreasonable Confidentiality/Non-publication Clauses: Art 7.6

The following outlines the thinking of the Working Committee regarding a corollary issue to the recommendations on investigator's/REB's TCPS duty to share new information that arises in the clinical trials setting (new article 7.5). Before turning to the corollary issue, it should be noted that much of the literature agrees that an investigator's duty to share new risk information on a timely basis is grounded on a paramount concern for patient safety, autonomy, informed consent, associated principles of doing no harm, a researcher's fiduciary duty and/or the principles of scientific integrity. Many also agree that the duty is overriding – that is, it tends to override contractual agreements that prevent the sharing or reporting of risk information.

To complement the Working Committee's recommendation for a clearer and more explicit investigator's duty to share information via a new article 7.5 in the TCPS, an important question arises: should the TCPS also directly address so-called “gag rules” – that is, confidentiality clauses or publication bans in industry/researcher contracts, which have come into prominence in recent years, as illustrated by the Olivieri affair?

After considering the rationales for and against doing so, the Working Committee recommends that the TCPS directly address this issue. Doing so would further the rationales behind an investigator's and REB's duty to share information, and would be directly responsive to recommendations in some of the Olivieri reports. It would provide important guidance to investigators, REBs and universities addressing such issues. It may contribute to policy development by other players such as government regulators and industry. Doing so would also likely enhance participants' welfare, rights and safety.

I. Existing TCPS Guidance

The existing guidance on this issue is found in the commentary to the Clinical Trials section. As the following excerpt indicates, the TCPS notes related issues and encourages researchers and REBs to resist efforts to hamper communications.

TCPS, Clinical Trials, Section 7, Subsection E

E. Analysis and Dissemination of Results of Clinical Trials (TCPS, p.7.5):

In many clinical trials, the sponsors obtain contractual rights to the initial analysis and interpretation of the resultant data. Researchers and REBs must ensure, however, that final analysis and interpretation of such data remain with the researchers, whose duty it is to ensure the integrity of their research....

Equally important, though sometimes difficult to achieve, is the researchers' duty to disseminate the analysis and interpretation of their results to the research community. Unfortunately, negative results and outcomes of research frequently are not published or disseminated. Silence on such results may foster inappropriate and potentially harmful clinical practices or needless and wasteful duplication. Researchers and REBs may exert pressure to alleviate this deficiency in the dissemination of research results by resisting publication bans proposed in research protocols, on the basis of ethical obligations of truthfulness and the integrity of research.

II. Points of Convergence and Commentary from Selected Reports

Our analysis of the different reports that have responded to the Olivieri affair indicate the following points of convergence. One of those points is that confidentiality clauses and publication restrictions may be acceptable, if they contain reasonable, justified, and not absolute restrictions.

- Primacy of patient safety and ensuring continuing consent
- Duty to disclose risks/information in the clinical trial setting
- Dissemination of research results to the scientific community
- Confidentiality clauses: acceptable if limited in time and scope
- Role of REBs: with respect to contracts
- Institutional support.

Excerpts from relevant related Canadian commentary on publication restrictions/confidentiality clauses:

CAUT Report, 2001

1..... *Certain circumscribed confidentiality restrictions may be appropriate, for example, those pertaining to information on the chemical structure, or synthesis of a drug, or its method of encapsulation. ... Restrictions on disclosures of risks to patients are not appropriate.*

Naimark Report, 1998 (Statements or Recommendations)

Part II *Introduction: University policies on contract research and conflict of interest* "...recognize both the primacy of the principle of free communication of research findings and the legitimate interests of industrial sponsors in protecting commercially valuable intellectual property." These two conflicting interests can be reconciled by providing a delay in publication sufficient to give the sponsor the opportunity to seek patent protection. "The University's policy states that the delay should never be longer than 12 months."

The Hospital for Sick Children Research and Policy Review Task Force Report, 1999

3.1.3: "The confidentiality provisions in contracts should be proportionate to the need for confidentiality."

3.1.4: "Contracts should include a provision which specifically allows the Hospital's REB to share and discuss information relating to multi-centre trials with other REBs reviewing the same protocol."

III. Selected Provisions from International Documents

A selected survey of leading international documents was conducted to collect relevant provisions regarding publication limitations and confidentiality clauses. They indicate that some of the documents address publication bans in a manner similar to the current TCPS, but with perhaps more force. We have identified two international policies that address the confidentiality clauses of investigator contracts, as done by Canadian reports in recent years. The International Conference on Harmonization and the new Directive on Clinical Trials from the European Union are silent on the issue. The U.S. FDA needs to be confirmed.

World Medical Association, *Declaration of Helsinki, 1964, as revised and clarified in 2002*

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interests should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research* (2005)

“Art. 28 Availability of results

... 3. The researcher shall take appropriate measures to make public results of research in reasonable time.”

The scope and intent of this article is discussed in the *Explanatory Report to the Draft Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research* (2004).

Article 28 Availability of results

135. Accountability is implicit in the relationship between the researcher and the participant. For this reason, this Article requires that the conclusions of the research be made available on request to research participants in a form comprehensible to them.

136. The Article requires researchers to submit a summary or report of the research to the ethics committee or competent body, and *to make public the results of their research even if the outcome is negative. Such results must be published or made otherwise available in a manner accessible to other researchers. The aim of the Article is to prevent the needless repetition of research using persons due to the non-publication of previous results, and to prevent the suppression of negative or positive results for commercial or other non-scientific reasons. It is stated that this be done “in reasonable time” so as to not prejudice a patent application or scientific publication. This obligation to publish cannot be restricted by contractual obligations* (emphasis added). However, under the terms of Article 26, paragraph 1, of the Convention, the obligation to publish research results would be waived if publication would potentially compromise, for example, public health or safety or the rights and freedoms of others. An example of such research could be that concerning counter-measures to the use of biological weapons, the publication of which could compromise public safety.

World Health Organization, *Operational Guidelines for Ethics Committees that Review Biomedical Research, TDR/PRD/ETHICS/2000.1, Geneva* (2000)

6.2 Elements of the Review

The primary task of an EC lies in the review of research proposals and their supporting documents, with special attention given to the informed consent process, documentation, and the suitability and feasibility of the protocol. ECs need to take into account prior scientific reviews, if any, and the requirements of applicable laws and regulations. The following should be considered, as applicable:

6.2.1 Scientific Design and Conduct of the Study

...

6.2.1.8 The manner in which the results of the research will be reported and published; ...

International Committee of Medical Journal Editors (ICMJE), *Statement on Conflicts of Interest* (2001)

Scientists have an ethical obligation to submit credible research results for publication. As the persons directly responsible for their work, researchers should not enter into agreements that interfere with their access to data independently, to prepare manuscripts and to publish them.

Pharmaceutical Research and Manufacturers Association (United States), *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results*, (2002)

Sponsors commit to “... not suppress or veto publications or other appropriate means of communication (in rare cases it may be necessary to delay publication and/or communication for a short time to protect intellectual property)...”

American Association of Medical Colleges/Baer I, Feiler ME, Regulski A, Switzer SS. *Clinical Trial Contracts: A Discussion of Four Selected Provisions*, (2004, pp. 7-8)

Publication is necessary for the Academic institution to fulfill its academic mission and disseminate the fruits of research. Research integrity is the cornerstone of the academic endeavor, and Academic institutions must demonstrate that research is being conducted in an unbiased manner, irrespective of the funding source... Some argue that research on human subjects that is not published is unethical; first, by needlessly exposing subjects to risk without benefit to general knowledge and second, by risking exposure of others because the research results are not available.

IV. Basic Options and Points to Consider for Framing a Recommendation

The Working Committee identified at least three options for addressing confidentiality and publication clauses within the current section 7 of the TCPS. They include (i) preserving the status quo; (ii) amending the existing commentary; or (iii) adopting a new article that addresses the matter. The merits of the issues and developments since 1998 persuaded the Committee to move beyond the status quo text of the TCPS in favour of the third option of a new article.

It was thus agreed that, consistent with the themes from the Olivieri reports noted in section II above, amongst the points to be included in a new TCPS article and accompanying commentary are the following:

- That confidentiality clauses or publication bans that impose absolute or unduly broad limitations should be presumed to be ethically unacceptable; and
- That institutions and REBs should develop an explicit written policy on confidentiality and publication bans affecting clinical trials.

Ethical Responsibilities and the Dissemination of Research Results

In its internal discussions and deliberations concerning a proposed amendment to the Ethics Framework, the Committee identified some key questions, such as the following:

- Whether articulation of this principle imposes a new ethical responsibility or makes explicit a long standing one;
- Whether the principle is one of academic freedom, of researchers' responsibilities, or both;
- Whether the principle might be used or enforced to impose inappropriate requirements on some research(ers);
- Whether the principle is disciplinary-based or shared by all disciplines.

To crystallize some of the key issues, the Committee has assembled the following sample of arguments pro and con.

Con: the principle

- outlines a new ethical obligation,
- is tantamount to a duty to publish, which is inappropriate for some research,
- is unlikely to be understood or correctly applied by REBs,
- risks infringing researchers' academic freedom, and
- is a biomedical research principle inappropriate to other kinds of research.

Pro: the principle

- is an established principle implicit within the concept of "research" (generalizable knowledge),
- is a basic principle of scientific or scholarly research,
- is integral to participants' expectation (and duty),
- is consistent with the ethics of transparency, and
- is public good.

The Committee has also sampled relevant documentation, e.g.:

Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research, 2005*

Art. 28 Availability of results ...

3. The researcher shall take appropriate measures to make public results of research in reasonable time.

Norway, National Committee for Research Ethics in the Social Sciences and the Humanities, *Guidelines for Research Ethics in the Social Sciences, Law and the Humanities, 2001*

3 The need for freedom of research

It is important to safeguard research against pressures which threaten to undermine the standards of the scientific method. Research activities must therefore be free in a particular sense: they must be safe from controls which prevent the posing of problems which appear contrary to economic, political and social interests, and from the suppression of results and conclusions....

38 Publication rights

The interests of the researcher in publication, and the demand for the verifiability of research, indicate the publication of research results.

Both public access to and the verification of research results are reasons why these should be published...

Canada, SSHRC, Research Data Archiving Policy

SSHRC is committed to the principle that the various forms of research data collected with public funds belong in the public domain. Accordingly, SSHRC has adopted a policy to facilitate making data that has been collected with the help of SSHRC funds available to other researchers.

American Sociological Association, *Code of Ethics*, 1999

13.04 Reporting on Research

(a) Sociologists disseminate their research findings except where unanticipated circumstances (e.g., the health of the researcher) or proprietary agreements with employers, contractors, or clients preclude such dissemination.

U.K. Social Research Association, *Ethical Guidelines*, 2003

(Obligations to Society)

1.1 Widening the scope of social research

Social researchers should use the possibilities open to them to extend the scope of social enquiry and communicate their findings, for the benefit of the widest possible community. ...

3.3 Communicating ethical principles

A principle of all scientific work is that it should be open to scrutiny, assessment and possible validation by fellow scientist.

Table of Concordance: TCPS and Proposed Recommendations

Original TCPS	January 2008 Version
<p>A. Clinical Equipoise B. Phases of Pharmaceutical Research C. Multicentre Clinical Trials D. Placebo-Controlled Studies E. Analysis and Dissemination of the Results of Clinical Trials</p> <p>Article 7.3</p> <p>REBs shall examine the budgets of clinical trials to assure that ethical duties concerning conflict of interest are respected.</p> <p>Budgets for clinical trials usually are calculated by per capita costs—that is, the sponsor pays the researcher a fixed sum for each research subject recruited. Per capita payments raise ethical concerns because of the potential to place the researcher in a conflict between maximizing economic remuneration and serving the best health interests of subject-patients, especially if the researcher also holds a therapeutic or clinical or other fiduciary relationship with the subjects. Disclosure of the amount of the per capita payment, and other budgetary details, will assist the REB in assessing potential conflicts of interest, and may also assist the researcher in resolving them. As a general guide, per capita payments should be comparable to the physician’s or researcher’s usual professional fee. When trials take place within a public institution, such as a hospital or a long-term care facility, recovery of utilization costs for institutional and other resources (such as radiological and diagnostic services) should be considered essential, and should be in addition to any overhead charge stipulated by the institution.</p> <p>Examination of the clinical trials within the ethical perspectives of the</p>	<p>A. Clinical Equipoise B. Phases of Pharmaceutical Research <u>C. Budgets, Contracts and Agreements</u> <u>D. Multicentre Clinical Trials</u> <u>E. Placebo-Controlled Studies</u> <u>F. Sharing New Information</u> <u>G. Analysis and Dissemination of the Data & Results of Clinical Trials</u></p> <p><u>C. Budgets, Contracts and Agreements</u></p> <p>Article 7.3</p> <p>REBs shall ensure that budgets, contracts and investigator agreements regarding clinical trials are properly examined to assure that ethical duties concerning conflict of interest are respected.</p> <p>Budgets for clinical trials are usually calculated by per capita costs— that is, the sponsor pays the researcher a fixed sum for each research subject recruited, <u>based on the length of time that the subject is on the study and the tests required by the trial. Unreasonable payments or undue inducements</u> raise ethical concerns because of the potential to place the researcher in a conflict between maximizing economic remuneration and serving the best health interests of subject-patients, especially if the researcher also holds a therapeutic or clinical or other fiduciary relationship with the subjects. Disclosure of the <u>kinds and amounts of the payments</u>, and other budgetary details, will assist the REB, <u>or other delegated body within the institution, to assess</u> potential conflicts of interest, and may also assist the researcher in resolving them. As a general guide, payments should be comparable to the physician’s or researcher’s usual professional fee <u>for the provision of comparable services</u>. When trials take place within a public institution, such as a hospital or a long-term care facility, recovery of utilization costs for institutional and other resources (such as</p>

phases outlined above for clinical trials will assist REBs and researchers in identifying ethical issues that are both generic for all clinical trials and specific for a given trial.

C. Multicentre Clinical Trials ...

D. Placebo-Controlled Studies ...

Article 7.4 The use of placebo controls...

radiological and diagnostic services) should be considered essential, and should be in addition to any overhead charge stipulated by the institution.

The independent review of the investigator-industry contract should be undertaken by a duly composed REB, or by or under the auspices of another competent institutional authority that shares the results with the REB, as an integral part of the ethics review process. If done under the latter process, the review of contracts should be conducted in a manner that: (i) conforms to the special ethical duties, mandate and purposes of REB review, and (ii) consults with the REB when necessary.

D. Multicentre Clinical Trials ...

E. Placebo-Controlled Studies ...

Article 7.4 The use of placebo controls...

F. Sharing New Information

Article 7.5

(a) If, in the course of a trial, new information arises that may be relevant to participants' free, informed and continuing consent to participation in the research, investigators should share the information, in a timely manner, with the REB and participants. The urgency of the timing should be commensurate with the potential seriousness of the risk raised by the information. In some circumstances, new information that arises after a trial may also need to be shared.

Article 7.5 outlines an investigator's continuing duty to share new and relevant information from the clinical trial process with the REB and research participants. "New information" is information that may affect the willingness of a participant to continue in the trial, or that is otherwise relevant to participants' free, informed, and continuing consent (See

articles 2.1, 2.4(f)). To understand its particular relevance, the information needs to be considered from a participant-centered perspective. This sharing may also include new information that arises outside the trial when that information is relevant to the participant's informed and continuing participation. "New information" thus covers a range of matters that include, but is not limited to, the following:

changes to the research protocol;

new risk information, such as adverse events or safety data;

new information which shows benefits of one intervention over another;

new findings, including important non-trial information;

unanticipated problems involving therapeutic efficacy or recruitment issues.

Duties to report such new information to the REB lies with the sponsor and the investigator. The REB's interdisciplinary advice should help structure the breadth and timing of sharing the information with participants. The more serious and urgent the information, the more promptly it should be shared.

In those circumstances when significant risk/benefit information arises after the trial, and which may well affect the well-being or safety of former participants, the investigator should share the information with the REB. The REB and investigator should consider whether given the nature and urgency of the information, a reasonable former participant would, under the circumstances, consider the information relevant to his or her well-being and informed choices. If so, then reasonable steps should be taken to share the information in a meaningful and timely manner with former participants.

In the event that a researcher and REB were to disagree over the sharing of new information with participants, attempts to resolve the disagreement should involve recourse to the REB appeals process (see articles 1.10-1.11, above). The REB process should be cognizant of, and sensitive to, the urgency of the matter. Attempts to resolve disagreement about the scope and reach of disclosure should be guided by a paramount principle of protecting the safety and welfare of trial participants.

(b) Nota: This proposed sub-article 7.5(b) outlines two options regarding a TCPS duty to share new clinical trials information with regulatory authorities. Both options address researcher and sponsor disagreement over reporting the new information to relevant regulatory authorities. Option A recognizes that the duty may arise, as a matter of professional conscience, given a number of factors. Option B outlines a special duty to report the information when a sponsor refuses to do so.

Option A (Good Conscience Clause): In exceptional instances of intractable disagreement, where all other reasonable measures have been exhausted, the principle of protecting the safety and welfare of patients should further guide researchers and REBs about the lengths to which they should go to share new, relevant and important information. If in good conscience, a researcher or REB, exercising independent and professional judgment, were to determine that sharing information likely would prevent significant harms to research participants, then the researcher or REB may reasonably conclude there is an ethical duty to do so, despite objections. The scope of the duty—what new information should be disclosed, when it should be disclosed, and to whom it should be disclosed—should be proportionate to the seriousness and urgency of the potential harm.

Option A addresses exceptional circumstances that might arise, for example, if a research sponsor were to refuse to report to a regulatory authority new and significant information. In such circumstances, should the researcher or REB report the new information to regulatory authorities? In their deliberations on such matters, researchers and REBs should consider such factors as: whether the information is novel and significant or duplicative; the objective quality and nature of the information; the direct relevance of the information to participants' safety, welfare and continuing consent; whether relevant entities (sponsors, data safety monitoring boards, and REBs) have been afforded a reasonable opportunity to discharge their duties with respect to the information, and relevant regulatory duties.

Option B (Special Duty to Report to Regulatory Authorities): In

E. Analysis and Dissemination of the Results of Clinical Trials

exceptional circumstances, beyond those required under existing regulations, the ethical principles of avoiding harm and respecting participants' informed consent impose on researchers or REBs a special duty to share new safety-efficacy information with regulatory authorities. When sponsors refuse to report new and significant information that is relevant to the safety and welfare of participants, then researchers and/or REBs have a duty to do so. The more objectively relevant and urgent the information, the stronger the duty. Before REBs or researchers act on such duties, they should afford sponsors a reasonable opportunity for reporting the information to the appropriate regulatory authorities.

G. Analysis and Dissemination of the Data and Results of Clinical Trials

Article 7.6

(a) Institutions and REBs should develop reasonable written policies regarding confidentiality clauses and publication clauses in research contracts between investigators and industry.

A reasonable institutional policy should:

require that confidentiality and publication clauses be submitted to the responsible authority (e.g. REB, research administration) for determination of their adherence to the written policy of the institution;

require that the results of the review be shared with the REB as an integral part of the ethics review process.

provide that all confidentiality and publication clauses:
be consistent with the investigator's duty to share new information from the clinical trial setting with REBs and trial participants in a timely manner, under articles 7.5 and 2.1(a);

be reasonable in terms of any limitations or restrictions on the dissemination or communication of information;

address data sharing/ownership; and

In many clinical trials, the sponsors obtain contractual rights to the initial analysis and interpretation of the resultant data. Researchers and REBs must ensure, however, that final analysis and interpretation of such data remain with the researchers, whose duty it is to ensure the integrity of their research. When stopping rules are required in Phase I, II and III clinical trials, monitoring of the interim results must be done independently. It should also be remembered that, with a stopping rule in place, long-term positive or negative effects might be masked by short-term harms or benefits.

Equally important, though sometimes difficult to achieve, is the researchers' duty to disseminate the analysis and interpretation of their results to the research community. Unfortunately, negative results and outcomes of research frequently are not published or disseminated. Silence on such results may foster inappropriate and potentially harmful clinical practices or needless and wasteful duplication. Researchers and REBs may exert pressure to alleviate this deficiency in the dissemination of research results by resisting publication bans proposed in research protocols, on the basis of ethical obligations of truthfulness and the integrity of research. Research journalists, journal editors, members of editorial peer review boards, sponsors and regulators should address this as an issue of scientific and ethical urgency.

address publication rights and authorship of the initial and subsequent reports in multicentre trials

(b) Absolute bans on the dissemination of scientific information from clinical trials are ethically unacceptable. Confidentiality clauses or publication limitations that impose unduly broad limitations on either the content of the scientific information that may be disseminated or on the timing of that dissemination are presumed to be ethically unacceptable.

In many clinical trials, the sponsors have contractual rights to the initial analysis and interpretation of the resultant data. These provisions are typically found in industry-investigator contracts that may not always be part of an REB review. To incorporate the analysis of these contractual provisions into modern interdisciplinary ethics review, articles 7.6(b) and 7.3 require (a) that institutions and REBs adopt reasonable written policies regarding such provisions; and (b) that contracts and relevant documents for proposed research be independently reviewed for their consistency with these policies and principles.

Article 7.6 is intended to ensure that any such contractual rights be reasonably balanced against the investigator's ethical and legal obligations to participants in trials and the scientific and public good in the dissemination of the data and results of research. For example, where stopping rules are in place, monitoring of the interim results must be done independently, for example, by an independent data safety monitoring board (DSMB). Properly composed and duly accountable DSMBs play an important role in ensuring independent overall analysis of clinical trial data and complement the role of the REB. It should also be remembered that, with a stopping rule in place, long-term positive or negative effects might be masked by short-term harms or benefits.

Measures necessary for the effective discharge of the duties of researchers' and institutions to share new information and disseminate the analysis and interpretation of their results to the research community may need to be undertaken. Based on principles of the scientific process, respect for participant expectations and protection of the public good, research

<p><i>Requirement for Free and Informed Consent</i></p> <p>Article 2.1</p>	<p><u>scientists and institutions have an ethical responsibility to make reasonable efforts to disseminate publicly the results of research in a timely manner.</u> Unfortunately, <u>however,</u> negative results and outcomes of research frequently are not published or disseminated. Silence on such <u>results may lead to data suppression and publication bias and thus contribute to a series of harms: misinformed decision-making based on a mis-weighing of risks and benefits, inappropriate and potentially harmful clinical practices and injury to health, needless and wasteful duplication of research interventions on participants, fraud or deception in the clinical trials process and erosion of public trust and accountability in research.</u> Research journalists, journal editors, members of editorial peer review boards, sponsors and regulators should <u>continue to</u> address this as an issue of scientific and ethical urgency. <u>Clinical trials registries, editorial policies, ethical policy reforms, and revised national and institutional ethics policies all contribute to a multi-faceted approach to combating the ills of non-disclosure and the suppression of data in clinical research.</u></p> <p>In the review process, the onus to justify significant restrictions <u>on dissemination</u> should lie on the researcher and, when appropriate, the sponsor. The reasonableness of the restrictions on either the content or timing of dissemination should be measured against the standards of the written institutional policies. For example, some existing university policies deem publication restrictions that exceed a reasonable time limit, e.g., <u>3-6 months after the close of the trial,</u> to be unacceptable. Such written institutional policies should also address restrictions on the dissemination of particular kinds of information, such as information that may be considered proprietary/trade secret and information that participants would reasonably consider relevant to their welfare or safety. Consistent with Articles 2.1 and 7.5, restrictions on the latter are seldom, if ever, justified.</p> <p>A. Requirement for Free, Informed <u>& Continuing</u> Consent</p> <p>Article 2.1</p> <p>Free and informed consent encompasses a process that begins with a</p>
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(a) Research governed by this Policy (see Article 1.1) may begin only if (1) prospective subjects, or authorized third parties, have been given the opportunity to give free and informed consent about participation, and (2) their free and informed consent has been given and is maintained throughout their participation in the research. Articles 2.1(c), 2.3 and 2.8 provide exceptions to Article 2.1(a).

(b) Evidence of free and informed consent ...

Free and informed consent lies at the heart of ethical research involving human subjects. It encompasses a process that begins with the initial contact and carries through to the end of the involvement of research subjects in the project. As used in this Policy, the process of free and informed consent refers to the dialogue, information sharing and general process through which prospective subjects choose to participate in research involving themselves.

Article 2.1(a) states the requirement in both ethics and law: to protect and promote human dignity. Ethical research involving humans requires free and informed consent. As elaborated more fully below, free and informed consent is exercised by an authorized third party for those who lack legal competence. ...

Article 2.4

Researchers shall provide, to prospective subjects or authorized third parties, full and frank disclosure of all information relevant to free and informed consent. Throughout the process of free and informed

researcher's initial contact with participants and which continues through to the end and sometimes beyond the research project. Throughout the process, researchers have a continuing duty to provide participants and REBs information relevant to the participant's free and informed consent to participate in the research.

(a) Research governed by this Policy (see Article 1.1) may begin only if:
(1) prospective subjects, or authorized third parties, have been given the opportunity to give free and informed consent about participation, and
(2) their free and informed consent has been given and is maintained throughout their participation in the research. Articles 2.1(c), 2.3 and 2.8 provide exceptions to Article 2.1(a).

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Article 2.4

Researchers shall provide, to prospective subjects or authorized third parties, full and frank disclosure of all information relevant to free and informed consent. Throughout the free and informed consent process,

consent, the researcher must ensure that prospective subjects are given adequate opportunities to discuss and contemplate their participation. Subject to the exception in Article 2.1(c), at the commencement of the process of free and informed consent, researchers or their qualified designated representatives shall provide prospective subjects with the following:

- (a) Information that the individual is being invited to participate in a research project;
- (b) A comprehensible statement of the research purpose, the identity of the researcher, the expected duration and nature of participation, and a description of research procedures;
- (c) A comprehensible description of reasonably foreseeable harms and benefits that may arise from research participation, as well as the likely consequences of non-action, particularly in research related to treatment, or where invasive methodologies are involved, or where there is a potential for physical or psychological harm;
- (d) An assurance that prospective subjects are free not to participate, have the right to withdraw at any time without prejudice to pre-existing entitlements, and will be given continuing and meaningful opportunities for deciding whether or not to continue to participate; and
- (e) The possibility of commercialization of research findings, and the presence of any apparent or actual or potential conflict of interest on the part of researchers, their institutions or sponsors.

...

the researcher must ensure that prospective subjects are given adequate continuing opportunities to discuss and contemplate their participation. Subject to the exception in Article 2.1(c), at the commencement of the free and informed consent process, researchers or their qualified designated representatives shall provide prospective subjects with the following:

- (a) Information that the individual is being invited to participate in a research project;
- (b) A comprehensible statement of the research purpose, the identity of the researcher, the expected duration and nature of participation, and a description of research procedures;
- (c) A comprehensible description of reasonably foreseeable harms and benefits that may arise from research participation, as well as the likely consequences of non-action, particularly in research related to treatment, or where invasive methodologies are involved, or where there is a potential for physical or psychological harm;
- (d) An assurance that prospective subjects are free not to participate, have the right to withdraw at any time without prejudice to pre-existing entitlements, and will be given continuing and meaningful opportunities for deciding whether or not to continue to participate; and
- (e) The possibility of commercialization of research findings, and the presence of any apparent or actual or potential conflict of interest on the part of researchers, their institutions or sponsors.

The measures to be undertaken to publish or otherwise make publicly available the results of the research.

...

...Article 2.4(f) requires that researchers provide a reasonable explanation of the measures to be undertaken to publish and otherwise disseminate the results of the research. Beyond the ethical obligation to do so in such areas as clinical trials (see articles 7.6(a) and 7.6(b) below), this requirement is grounded on the reasonable expectation of participants in research that the results will be published or otherwise disseminated in the public domain to advance societal knowledge.

Table 1: Additional information that may be required for some projects

1. ...

10. The ways in which the research results will be published, and how the subjects will be informed of the results of the research.

B1. Authority of the REB

Article 1.2

The institution in which research involving human subjects is carried out shall mandate the REB to approve, reject, propose modifications to, or terminate any proposed or ongoing research involving human subjects that is conducted within, or by members of, the institution, using the considerations set forth in this Policy as the minimum standard.

The authority of the REB should be delegated through the institution's normal process of governance. In defining the REB's mandate and authority, the institution must make clear the jurisdiction of the REB and its relationship to other relevant bodies or authorities. Institutions must ensure that REBs have the appropriate financial and administrative

Table 1: Additional information that may be required for some projects

1. ...

10. How the subjects will be informed of the results of the research.

B1. Purpose and Authority of the REB

Article 1.2

(a) The primary purpose of REB review is to protect the dignity, well-being, rights and safety of research participants.

(b) The institution in which research involving human subjects is carried out shall mandate the REB to approve, reject, propose modifications to, or terminate any proposed or ongoing research involving human subjects which is conducted within, or by members of, the institution, using the considerations set forth in this Policy as the minimum standard.

Article 1.2(a) indicates the primary purpose of human research ethics review. Respecting the dignity and protecting the rights of participants reflect fundamental values in research ethics. Those values will sometimes conflict with others, such as the societal good that may derive from research. The value conflict is endemic in REB review, as recognized in the ethics framework of the TCPS. Under the framework, the functions of REB review need to be exercised and applied thoughtfully to diverse research contexts. Those contexts range from the safety risks posed by health science research to critical social sciences research the purpose of which is to critique those under study.

The authority of the REB should be delegated through the institution's normal process of governance. In defining the REB's mandate and authority, the institution must make clear the jurisdiction of the REB and its relationship to other relevant bodies or authorities. Institutions must ensure that REBs have the appropriate financial and administrative

independence to fulfil their primary duties. ...

F. Review Procedures for Ongoing Research

Article 1.13

(a) Ongoing research shall be subject to continuing ethics review. The rigour of the review should be in accordance with a proportionate approach to ethics assessment.

(b) As part of each research proposal submitted for REB review, the researcher shall propose to the REB the continuing review process deemed appropriate for that project.

(c) Normally, continuing review should consist of at least the submission of a succinct annual status report to the REB. The REB shall be promptly notified when the project concludes.

Beyond scrutinizing reports, the REB itself should not normally carry out the continuing ethics review, except in specific cases where the REB believes that it is best suited to intervene. For research posing significant risks, the REB should receive reports on the progress of the research project at intervals to be predetermined. These reports should include an assessment of how closely the researcher and the research team have complied with the ethical safeguards initially proposed.

In accordance with the principle of proportionate review, research that exposes subjects to minimal risk or less requires only a minimal review process. The continuing review of research exceeding the threshold of minimal risk that is referred to in Article 1.13(b), in addition to annual review (Article 1.13(c)) might include:

independence to fulfil their primary duties. ...

F. Review Procedures for Ongoing Research

Article 1.13

Ongoing research shall be subject to continuing ethics review. The rigour of the review should be in accordance with a proportionate approach to ethics assessment.

As part of each research proposal submitted for REB review, the researcher shall propose to the REB the continuing review process deemed appropriate for that project.

Normally, continuing review should consist of at least the submission of a succinct annual status report to the REB. The REB shall be promptly notified when the project concludes.

As part of continuing ethics review, researchers should fulfill their responsibilities for continuing consent and the reporting of new information that arises in clinical trials, consistent with articles 2.1 and 7.5.

Beyond scrutinizing reports, the REB itself should not normally carry out the continuing ethics review, except in specific cases where the REB believes that it is best suited to intervene. For research posing significant risks, the REB should receive reports on the progress of the research project at intervals to be predetermined. These reports should include an assessment of how closely the researcher and the research team have complied with the ethical safeguards initially proposed.

In accordance with the principle of proportionate review, research that exposes subjects to minimal risk or less requires only a minimal review process. The continuing review of research exceeding the threshold of minimal risk that is referred to in Article 1.13 (b), in addition to annual review (Article 1.13 (c)) might include:

Formal review of the process of free and informed consent;
Establishment of a safety monitoring committee;
Periodic review by a third party of the documents generated by the study;
Review of reports of adverse events;
Review of patients' charts; or
A random audit of the process of free and informed consent.

Other models of a continuing ethics review may be designed by researchers and REBs to fit particular circumstances.

The process of a continuing ethics review should be understood as a collective responsibility, to be carried out with a common interest in maintaining the highest ethical and scientific standards. Research institutions should strive to educate researchers on the process of a continuing ethics review through workshops, seminars and other educational opportunities.

TCPS Ethics Framework

E. Academic Freedoms and Responsibilities

Researchers enjoy, and should continue to enjoy, important freedoms and privileges. To secure the maximum benefits from research, society needs to ensure that researchers have certain freedoms. It is for this reason that researchers and their academic institutions uphold the principles of academic freedom and the independence of the higher education research community. These freedoms include freedom of inquiry and the right to disseminate the results thereof, freedom to challenge conventional thought, freedom from institutional censorship, and the privilege of conducting research on human subjects with public monies, trust and support. However, researchers and institutions also recognize that with freedom comes responsibility, including the responsibility to ensure that research involving human subjects meets high scientific and ethical standards. The researcher's commitment to the advancement of knowledge also implies duties of honest and thoughtful inquiry, rigorous analysis, and accountability for the use of professional standards. Thus, peer review of research proposals, the findings and their interpretation contribute to

Formal review of the free and informed consent process,
Establishment of a safety monitoring committee,
Periodic review by a third party of the documents generated by the study,
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<p>accountability, both to colleagues and to society.</p> <p>Review of the ethics of research helps ensure a more general accountability to society. Accountability, moreover, requires that the whole process should always be open to critical assessment and debate.</p>	<p><u>make reasonable efforts to disseminate or otherwise make publicly available the results of research, in a manner respectful of disciplinary and cultural contexts.</u></p> <p>Peer review of research proposals, <u>research</u> findings and their interpretation contribute to accountability, both to colleagues and to society. Review of the ethics of research helps ensure a more general accountability to society. Accountability, moreover, requires that the whole process should always be open to critical assessment <u>and scientific and public</u> debate.</p>
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