
**Harmonisation of the *Tri-Council Policy Statement:
Ethical Conduct for Research Involving Humans (TCPS)*
and *ICH-Good Clinical Practice:*
Conflict or Clarification?**

Submitted by the

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November 2007



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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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Executive Summary

Even before the official release of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS), concern was raised that there may be important differences between the TCPS and the *International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use Guidance E6: Good Clinical Practice: Consolidated Guideline* (ICH-GCP). It was thought that these documents were not fully aligned with each other, and thus researchers and REBs, might not be compliant with Health Canada regulations if they adhered solely to the TCPS. After study and analysis, the Harmonisation Initiative Committee identified no actual conflicts between the TCPS and ICH-GCP. Issues identified as possible discrepancies were determined to be related to topics on which the TCPS was either silent or nonspecific.

In an effort to provide clarification, the Committee has included textual changes in its report. Note that the textual changes offered in this document as “possible modifications” are meant to be suggestions only and are provided to enhance the understanding of the recommendations or conclusions.

1. Introduction

As early as 1996, concern was raised that there may be important differences in the early drafts of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS)¹ and Canadian and international regulatory requirements, particularly the *International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use Guidance E6: Good Clinical Practice: Consolidated Guideline* (ICH-GCP)² adopted by Health Canada. It was thought that these documents were not fully aligned with each other, and thus researchers and REBs might not be compliant with Health Canada regulations if they adhered solely to the TCPS.

2. Development, Use & Status of the Documents

2.1 The TCPS

In 1998, Canada's three funding agencies: the Canadian Institutes of Health Research (CIHR)³, the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC) adopted the TCPS as a common policy standard for those conducting, participating in, or reviewing human research under the auspices of institutions funded by CIHR, NSERC or SSHRC. The TCPS is a set of guidelines that is interdisciplinary in nature in order to reflect the respective domains of the three Agencies. It is to be considered the minimum standard⁴ for the ethical review of research involving humans.

In order to receive funding from any of these agencies,⁵ institutions are required to develop institutional policies on the ethical conduct of research involving humans consistent with the TCPS. The TCPS is intended to assist research ethics boards (REBs), researchers, REB administrators and research participants to understand and apply standards and procedures that relate to the ethics review process.

The Agencies intended the TCPS to be a “living document” and for it to evolve as needed. In late 2001 the three Agencies created the Interagency Advisory Panel and Secretariat on Research Ethics (PRE/SRE). Part of PRE's mandate⁶ is to support the development and evolution of the TCPS. PRE subsequently created the Sub-Group on Procedural Issues for the TCPS (ProGroup) in March 2003, to identify gaps and procedural issues in the TCPS that warrant revision.

2.2 The ICH-GCP

The ICH Good Clinical Practice (ICH-GCP) document is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. The 1996 ICH-GCP document was the result of a joint initiative of regulators and industry representatives from Japan, the European Union and the US with several “observer status” organizations including Health Canada.

This guidance was developed with the aim of strengthening protections for human research participants and to promote the development and registration of safe, effective, and high quality

¹ Web link to the TCPS <http://www.pre.ethics.gc.ca/english/policystatement/policystatement.cfm>

² Web link to the ICH-GCP <http://www.ich.org/LOB/media/MEDIA482.pdf>

³ The former Medical Research Council of Canada (MRC) was an original author. In 2000, the Government of Canada created CIHR and the MRC was dissolved.

⁴ Please see TCPS Article 1.2, p. 1.2.

⁵ Web link to the Memorandum of Understanding http://www.nserc.ca/institution/mou_e.htm

⁶ Web link to PRE's mandate <http://www.pre.ethics.gc.ca/english/aboutus/mandate.cfm>

drugs in a standardized efficient manner. The ICH-GCP guidance was adopted by Health Canada in 1997.

Compliance with the principles and details of good clinical practices was expected from sponsors who intended to submit data to Health Canada in support of new drug submissions (marketing applications) and as general guidance for the conduct of clinical trials. In 2001, regulatory amendments were introduced into the legislation for clinical trials in Canada (Part C, Division 5 of the Food and Drug Regulations⁷). The principles of good clinical practices are specifically referenced in Division 5. The ICH-GCP impacts on the work of REBs as it describes requirements for REB operations and records. The assumption on the part of Health Canada inspectors and trial sponsors is that the ICH-GCP guides the conduct of clinical trials in Canada. In addition, it should be noted that the acceptability of Canadian research data in submissions to foreign regulators, such as the US Food and Drug Administration, is based on compliance with ICH-GCP.

3. Harmonisation Initiative

The TCPS and ICH-GCP harmonisation issue was initially examined by the Medical Research Council (MRC), the predecessor to CIHR, by the MRC Taskforce on Research Ethics Boards and Clinical Trials in 1998. It was further explored in February 1999 by participants at the “Workshop on Research Ethics: Maximizing Effectiveness” and again in January 2000 at a meeting of the Stakeholders' Working Group on Best Practices for Industry-Academe Interactions, both sponsored by the Medical Research Council. When CIHR replaced the MRC in 2000, the issue was not pursued although it was the topic of discussion at meetings of the CIHR Standing Committee on Ethics between 2002 and 2005. With the creation of PRE in late 2001, the possible conflicts and lack of specificity in the TCPS were again identified as an issue. Upon ProGroup’s creation in early 2003, public consultations were held to identify what the research community viewed as the most pressing procedural and definition issues in the TCPS to be addressed. The “harmonisation of the ICH-GCP and TCPS” was identified as the fourth most important area behind proportionate review, continuing ethics review of ongoing research and multicentred ethics review.

Early in 2006, a subcommittee of ProGroup was formed with membership from Health Canada, the pharmaceutical industry, ProGroup and SRE, and was named the Harmonisation Initiative Committee (HI-C). The mandate of the group was to identify whether there were actual conflicts between the TCPS and the ICH-GCP; and to suggest solutions. This paper presents the findings of the HI-C for consideration and comment.

4. Process and Methodology

Canada’s Research-Based Pharmaceutical Companies (Rx&D) submitted to PRE a list of issues that they felt required attention to address the perceived differences between the TCPS and the ICH-GCP.⁸ HI-C used this comprehensive document as the starting point of its assessment. The committee also reviewed the TCPS and ICH-GCP in detail to identify additional areas that needed consideration.

⁷ Web link to Part C Division 5 of the Food and Drug Regulations:
http://laws.justice.gc.ca/en/showdoc/cr/C.R.C.-c.870/bo-ga:l_C::bo-ga:l_D//en?page=2

⁸ HI-C thanks Canada’s Research-Based Pharmaceutical Companies (Rx&D) for their contributions, in particular the input of Ms. Marianne Vanderwel who has championed the issue of harmonisation since 1996 and who provided a comprehensive compilation of key areas in the TCPS that posed potential discrepancies with the ICH-GCP.

The TCPS and the ICH-GCP are not the only Canadian documents that guide the conduct of clinical trials. As stated above, Part C, Division 5 of the Food and Drug Regulations, its related regulations and guidance, and provincial and federal privacy legislation also affect, to some degree, REB operations, and researcher and sponsor responsibilities.

HI-C limited the scope of its assessment to the TCPS, ICH-GCP and Part C, Division 5 of the Food and Drug Regulations. Issues relating to privacy and conflict of interest also identified by Rx&D as possibly needing clarification in the TCPS were beyond the scope of HI-C's mandate and are already addressed by *Personal Information Protection and Electronic Documents Act* (PIPEDA), provincial privacy legislation, or other PRE working committees. For example, obligations to report results especially of a serious nature, is not detailed in the TCPS. However, as PRE's Clinical Trials Information Working Committee has examined reporting obligations by investigators and REBs to sponsors and/or regulatory authorities, HI-C did not replicate this work.

5. Issues, Findings & Recommendations

5.1 Summary

HI-C identified no actual conflicts between the TCPS and ICH-GCP. The issues identified were generally related to topics on which the TCPS was either silent or nonspecific. It should be noted that some of this lack of specificity in the TCPS may have been deliberate to ensure the TCPS remained applicable to all research domains.

In developing its recommendations, HI-C was mindful that ICH-GCP and Part C, Division 5 of the Food and Drug Regulations pertain to clinical drug trials only. Not all clinical trials are conducted for this purpose.

For the TCPS to remain relevant to all research in the domains of the Agencies, special care must be taken not to impose clinical trial-related language or conditions on the document in areas meant to provide general guidance. Therefore, HI-C worked within the principle that any proposed modifications to the body (Sections 1-5) of the TCPS should remain generic whenever possible. Specific recommendations relating solely to clinical trials (e.g. regulatory requirements and international standards) would be addressed in Section 7 of the TCPS which is dedicated to clinical trial issues.

Note that the textual changes offered in this section as "possible modifications" are meant to be suggestions only and are provided to enhance the understanding of the recommendations or conclusions.

5.2 Reference to the ICH-GCP

Issue: No specific reference to the status of the ICH-GCP in the TCPS.

The issue centres on whether or not the TCPS should contain an explicit reference to the ICH-GCP that identifies the ICH-GCP as a required set of policies and procedures.

The ICH-GCP is referenced in Section 7 (para 5 page 7.3) of the TCPS:

"Clinical investigators undertaking research intended for use in seeking regulatory approval for pharmaceuticals should also generally respect the ICH Guidelines, which were developed by the United States, Europe and Japan and have been adopted by Canada."

However the inclusion of the word “generally” has been interpreted by some as negating the requirement to consider and comply with the ICH-GCP when dealing with clinical trials.

Conclusion: Clarification of the TCPS desirable.

Recommendations:

- Revision to the reference to the ICH-GCP in the commentary relating to Article 7.2 to remove ambiguity as to the applicability of the ICH-GCP.

Possible modification - Example #1

Commentary to Article 7.2 (last paragraph) – revision to text

Clinical investigators undertaking research intended for use in seeking regulatory approval for pharmaceuticals must comply with Health Canada regulations and should also ~~generally~~ respect the ICH Guidelines, which were developed by the United States, Europe and Japan and have been adopted by Canada.

- Textual changes to Article 1.1(a) to indicate that researchers are also obligated to adhere to all other laws, regulations or guidance that may apply to the research in question.

Possible modification - Example #2

Article 1.1 – revision to text

All research that involves living human subjects requires review and approval by an REB in accordance with this Policy Statement, and all applicable legislative and regulatory requirements before the research is started, except as stipulated below.

- An addition to the Commentary for Article 1.1 to direct users to Section 7 for clinical trial-related guidance.

Possible modification - Example #3

Commentary to Article 1.1 – additional text

When generating clinical data that are intended to be submitted to regulatory authorities, specific requirements as to the roles and responsibilities of the REB are more precisely defined in other documents. Further guidance on clinical trials can be found in Section 7.

5.3 REB Roles and Responsibilities

5.3.1 Issue: The roles and responsibilities of the REB along with those of the researcher and sponsor are specifically indicated in the ICH-GCP but not in the TCPS. The lack of specificity in the TCPS is used by some as a rationale for avoiding their responsibilities.

Conclusion: Clarification of the TCPS desirable.

REB operations were identified as needing development in ProGroup’s 2003 public survey. Work in this area has been initiated by ProGroup and will specifically address the roles and responsibilities of the REB in more detail. HI-C will not duplicate this work, but will ensure that

ProGroup is cognizant of GCP requirements. The Clinical Trials Information Working Committee will also be addressing, in part, the role of the REB.

5.3.2 *Issue:* The TCPS does not clarify the issue regarding use of independent REBs for researchers outside of an institution.

The TCPS applies to all research conducted by members of, or under the auspices of, institutions eligible to administer funding from the Agencies. The Agencies have no regulatory duties or powers and thus have no jurisdiction over REBs that are not part of these institutions.

Conclusion: This is beyond the mandate of HI-C and PRE, and outside the jurisdiction of the Agencies. Clarification of TCPS would be required in the future if the TCPS was formally adopted as the standard for the ethical review of all research involving humans in Canada.

5.4 Operating Procedures

Issue: The establishment and documentation of operating procedures are specifically indicated in the ICH-GCP but not in the TCPS. The lack of specificity in the TCPS is used by some as a rationale for not having formal written procedures.

Conclusion: Clarification of the TCPS required.

Recommendations have been made to add to the commentary related to Article 1.2. This issue and the recommended textual changes will be examined further by ProGroup as part of their work on REB operations.

Possible modification - Example #4 **Commentary to Article 1.2 – additional text**

Institutions should ensure that the REB establish written standards and procedures which adhere to the TCPS and all guidelines and requirements which apply to the research under review. These standards and procedures should be readily available to all research stakeholders and should detail the documentation required in a submission to the REB.

5.5 Proportionate Review

Issue: While the TCPS outlines requirements for full REB review, it does not provide much guidance for expedited review. The TCPS does not require REBs to establish or make publicly available their policies and procedures relating to expedited review.

Conclusion: Clarification of the TCPS required.

ProGroup's work on proportionate review will result in significant changes in the TCPS regarding the proportionate review process. ProGroup specifically recommends that institutions have formal guidelines or policies relating to delegated (expedited) review and make them publicly available.

5.6 Description of Members and Quorum

Issue: The ICH-GCP and Division 5 of the Food and Drug Regulations have specific requirements for REB membership and quorum but the TCPS does not acknowledge the requirement for adherence to other requirements mandated by other authorities.

It is important to reiterate that the TCPS recommendations are the minimal standards for REB membership and quorum respectively and do not preclude or restrict REB membership to only those listed in the TCPS.

Conclusion: Clarification of the TCPS desirable.

HI-C has recommended that there be textual changes to the commentary for Articles 1.3 and 1.7. This issue and the proposed textual changes will be examined further by ProGroup as part of their work on REB operations.

Possible modification - Example #5 **Commentary to Article 1.3 – additional text**

The majority of members of an REB should have the qualifications, training and the expertise to make sound judgments on the ethics of research proposals involving human subjects. Copies of curriculum vitae of REB members should be retained by the REB and updated regularly. All REBs should have a training program for new members as well as an ongoing training program for existing members. Participation in training should be documented and records should be retained by the REB. Other regulatory requirements as to REB membership and evidence of member qualifications must also be accommodated when appropriate.

Possible modification - Example #6 **Commentary to Article 1.7 – revision to text**

Regular attendance by REB members at meetings is important, and frequent unexplained absences should be construed as a notice of resignation. Institutions should also establish quorum rules for REBs. The REB should make its decisions at announced meetings at which at least a quorum is present and maintained throughout the meeting. ~~When there is less than full attendance, &~~ Decisions requiring full review should be adopted only if the members attending the meeting possess the range of background and expertise stipulated in Article 1.3.

5.7 Results and Notification of REB Review

Issue: The TCPS is not sufficiently specific about mechanisms for notification of the results of REB review. This process is outlined in detail in the ICH-GCP.

Conclusion: Clarification of the TCPS desirable.

HI-C recommends that there be textual changes to the commentary of Article 1.9 to clarify the issue. This will assist REBs in ensuring their documentation is adequate. This issue and the recommended textual changes will be examined further by ProGroup as part of its work on REB operations.

Possible modification - Example #7
Commentary to Article 1.9 – additional text

REB decisions should be supported by clear references (e.g. date of decision, title of project), basis for decision (i.e. documents received and reviewed), plan for continuing ethics review and timelines, reasons for decisions and any conditions or limitations attached to the approval.

5.8 Record Retention

Issue: The TCPS does not provide guidance as to time periods for retention of documents, or what documents should be kept. The ICH-GCP does provide some guidance.

In May 2006, Health Canada released a document entitled *Guidance for Records Related to Clinical Trials: Guide 0068 Interpretation of section C.05.012 of the Food and Drug Regulations - Division 5 “Drugs for Clinical Trials Involving Human Subjects”*⁹ which details what should be kept, by whom and for how long. This guidance will assist those involved with clinical trials that require approval from regulatory authorities in determining their responsibilities with regard to record retention.

Conclusion: Clarification of the TCPS desirable.

HI-C recommends that there be textual changes to Article 1.8 and the commentary to Article 1.8 to recognize the need to be cognizant of other institutional, regulatory and/or discipline-specific retention requirements.

Possible modification - Example #8
Article 1.8 – additional text

Minutes of all REB meetings shall be prepared and maintained by the REB. The minutes shall clearly document the REB's decisions and any dissents, and the reasons for them. The documents received and reviewed by the REB should be clearly referenced in the REB's formal notice of decision to identify the basis on which the decision was made. In order to assist internal and external audits or research monitoring, and to facilitate reconsideration or appeals, the minutes and other related records must be accessible to authorized representatives of the institution, researchers, funding agencies and sponsors when applicable.

Possible modification - Example #9
Commentary to Article 1.8 – additional text

The REB should maintain general records related to membership, qualifications of members, procedures for the conduct of reviews for the approval of research and a copy of its minutes. These records should be retained at least until all research studies relating to these records and referenced in the minutes have been completed for a minimum of 3 years. It is recommended that REBs also maintain individual records relating to a specific study. Study specific records should be retained for a minimum period of 3 years after a study is closed keeping in mind that institutional, regulatory or other requirements may necessitate longer periods of retention.

⁹ Web link for Health Canada Guidance for Records Related to Clinical Trials: Guide 0068
http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui_68_tc-tm_e.html

5.9 Changes to ongoing research

Issue: The ICH-GCP is very specific in its requirements for REB approval of changes to a ongoing research protocol. However, the expectation that researchers will obtain REB approval for changes to approved research is not explicitly stated in the TCPS. The lack of specificity in the TCPS is used by some as a rationale for avoiding this requirement.

Conclusion: Clarification of the TCPS required.

This issue was identified in ProGroup's 2003 community consultation and recommendations are currently being prepared through ProGroup's Continuing Ethics Review initiative. HI-C did not duplicate this work.

5.10 Reports

Issue: The TCPS does not adequately deal with the requirement for and assessment of progress reports and reports of results.

Conclusion: Clarification of the TCPS required.

This issue is being specifically addressed by ProGroup in its analysis of issues relating to continuing ethics review of ongoing research.

5.11 Informed Consent

5.11.1 Informed Consent Process

Issue: The ICH-GCP is very detailed in its requirements relating to the informed consent process but the TCPS is less specific. The lack of specificity in the TCPS is used by some as a rationale for avoiding these requirements.

Conclusion: Clarification of the TCPS desirable.

This issue is being partially addressed by the Clinical Trials Information initiative. HI-C will not duplicate this work. HI-C recommends that there be textual changes to the commentary of Article 2.1.

Possible modification - Example #10 **Commentary to Article 2.1– additional text**

Article 2.1(b) states the preference for written evidence of free and informed consent. The article acknowledges that written consent is not always appropriate. For most people in our society, a signed statement is the normal evidence of consent. However, for some groups or individuals, a verbal agreement, perhaps with a handshake, is evidence of trust, and a request for a signature may imply distrust. Nonetheless, in most cases a written statement of the information conveyed in the consent process, signed or not, should be left with the subject. In some types of research, oral consent may be preferable. In others, written consent is mandatory and a witness may be required. (See Article 2.4) Where oral consent is appropriate, the researcher may wish to make a contemporaneous journal entry of the event and circumstances.

5.11.2 Compensation

Issue: The ICH-GCP is very detailed in its requirements relating to the notification of compensation in the informed consent process but the TCPS is less specific. The lack of specificity in the TCPS is used by some as a rationale for avoiding these requirements.

Conclusion: Clarification of the TCPS desirable.

HI-C recommends a textual change to Table1 to clarify the compensation issue.

Possible modification - Example #11

Article 2.4, Table 1, Item 7 – additional text

Information on any costs, payments, reimbursement for expenses or compensation and/or treatment for injury;