A Comparative Analysis of Process Requirements for Canadian Research Participant Protection Programs (RPPP)

SUPPLEMENTARY REPORT
March 17, 2014

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1. SCOPE AND LIMITS

This Comparative Analysis (also referred to as the “Report” throughout) is a supplement to the 2007 and 2004 Comparative Analysis reports.

For 2014, the Comparative Analysis has been updated to include two documents:
   i) The Tri-Council Policy Statement, 2010 (“TCPS2”); and

The mandate for creating this 2014 Report was limited in scope to adding relevant materials from the TCPS2 and the Standards only, and did not include review of, or corresponding updates related to, other documents. Specifically, entries in the Appendices about the following documents, which are known to have changed since 2007, have not been reviewed or updated in this 2014 Report:
   i) WHO Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants, (WHO Standards) (2011);
   ii) The Declaration of Helsinki (2013);
   iii) Provincial and/or territorial statutes/regulations, or any amendments to existing provincial and/or territorial statutes/regulations (e.g., the Québec Civil Code).

The review of the TCPS2 and the Standard resulted in changes to the categories of procedural elements used for the analysis. An overview of these categories of elements (and sub-elements) was included in the 2004 and 2007 reports in Appendix A. In this 2014 Report, modifications made to the elements have been noted in blue font; see Appendix A. For example, category 1 “Enabling Elements of Research Ethics Review” previously included the sub-element of “1.2 Development of Local Policies”, which has now been expanded to “1.2 Development of Local Policies/Agreements”, to reflect requirements in the TCPS2 and the Standards related to agreements. The rationale for making these modifications included that at least one of either the TCPS2 or the Standards presented a new kind of requirement that did not fit well within any existing categories.

For clarity, entries in the tables in Appendix B have been dated “doe 02-2014” (i.e., the date of entry (“doe”) of February 2014 for the TCPS2 and the Standard) or “2007” (for entries yet to be updated.) This new material appears in blue font. Because this 2014 Report is only a partial update to the 2007 and 2004 reports, readers should be cautious when using the Appendix B tables, as updating only a limited number of normative documents may mislead. For documents known to have been modified or repealed, the corresponding text appears in gray font. (However, once again, the substance of any related changes have not been reviewed or noted in the current Report.)

As noted under section 4 of this Report, “Recommendations, Conclusions and Next Steps”, because of the limits on activities conducted for the 2014 update, this version of the Comparative Analysis is of limited value. If conducted in the near future, a complete and comprehensive update will
ensure the utility, reliability and credibility of the Comparative Analysis as a reference tool. As was conducted for both the original 2004 and 2007 reports, a complete and comprehensive update will require a thorough policy and legal search. These future updates may serve to review or to add further expanded categories of elements and/or sub-elements used for the matrix in Appendix A. This kind of robust review will also serve to identify new documents that should be included.

In this regard, section 4 below includes specific examples of documents that are known to have been introduced, modified, or declared no-longer-in-force since 2007. These examples serve to illustrate the limits on the current 2014 Comparative Analysis.

As with the previous 2007 and 2004 reports, the 2014 Report focuses on baseline process requirements that apply to research in general involving adults who are competent to consent, irrespective of the type of research. This excludes specific requirements developed for research involving minors, incompetent adults, or again, for certain kinds of research, such as genetic research, or biobanking. Rather, the focus is on procedural aspects, not on substantive issues, unless they are intimately linked to a process requirement. The importance of procedural aspects is reflected in Hadcis

“[N]o less crucial are the procedures that are employed throughout the REB decision-making process. Decision outcomes, parties’ perceptions about whether they have been treated fairly and public confidence in the research governance regime are all potentially affected by the procedures REB follow.”

2. METHODOLOGY

The approach to updating the 2014 Report was as follows:

- Using the matrix of procedural elements and sub-elements in Appendix A, as well as the corresponding descriptions in the main body of the 2007 Report, we reviewed the TCPS2 and the Standards and identified and extracted all research participant protection programme (RPPP) process requirements;
- As described earlier in part 1, “Scope and Limits”, we modified and/or expanded some categories of elements/sub-elements in Appendix A (also reflected in Appendix B), as the documents reviewed revealed some new elements or sub-elements that could not be accurately included within the existing options;
- We reviewed a collection of interpretations about the TCPS2 by the Panel on Research Ethics (PRE) for any clarification on procedural issues;
- We conducted a literature search and review, included corresponding new citations in the bibliography, and incorporated relevant findings into our analysis in the 2014 Report; and
- We created the current main 2014 Report, which serves as a supplement to the 2007 Report, with an analysis that focuses on the key findings of the two documents reviewed, as well as recommendations for next steps.

1 Hadcis, 2011, 350.
3. ANALYSIS OF PROCESS REQUIREMENTS

The current 2014 Report serves as a supplement to the 2007 report. As noted in part 1, "Scope and Limits", the focus is on key issues related to the TCPS2 and Standard, with more pinpointed comments provided in the tables of Appendix B Tables within the “comments” column. Some of the comments are discussed below in section 3.

The sub-headings in part 3 of the Report bring attention to selected themes identified during the review of the TCPS2 and the Standard. Some themes bring new elements and observations to the Comparative Analysis, or speak to a gap identified in the earlier 2004 or 2007 versions, while others are shown to be in tension with other documents already included from earlier versions.

3.1 Overall “programme” assessment

Both the 2004 and 2007 versions of the Comparative Analysis presented and compared various normative documents. The comparisons involved, for example, assessing consistencies and inconsistencies between documents, as well as considering the effectiveness of each set of requirements for ensuring protection of participants. Assessing the effectiveness of mechanisms for ensuring protections was the most challenging concern, because it involved identifying what requirements are missing, and because the criteria and tools for determining those requirements are vague. Whether the focus is on RPPPs at the institutional level, or RPPPs as part of the broader Canadian “system” for ensuring research participant protection, several issues remain. Commentary on many of these issues was previously included in the 2004 and/or 2007 reports, however, the discussion below is limited to issues and concerns that persist, are new, or have been resolved via review of the TCPS2 and the Standard.

3.1.1 Complex normative landscape

The normative landscape of RPPPs continues to be a complex patchwork of regulations, guidelines, policies, stakeholders and procedures. Applicable norms depend on a number of factors such as whether they involve regulated products, where the research is conducted in terms of province/territory or private/public institutions, the source of funding and the profession of the researcher. Depending on factors such as these, a selection of norms will apply to a given project, but not to another. From a participant’s point of view, this may mean that participation in research might be tightly regulated, or barely so. Of course, trials with federally regulated products are an exception.

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3 McDonald et al, 2011, p. 36.: “It may seem strange to talk about a Canadian governance system for (human) health research because “system” is a term that seems ill suited to the complex set of standards, policies, procedures and practices that constitute participant protection in Canadian health research. There are macro-level actors who set general parameters (including governments, professional bodies and research sponsors), meso-level institutions (research institutions, sites where research is conducted) and individuals (including researchers and research workers). Moreover, there is an array of actual and potential authorities for Canadian research protection – international, federal, provincial, institutional and professional – as well as a complex mix of domestic and international interests and interest groups – commercial, public, consumer, political, etc. that often act at cross purposes. Despite these complexities, we believe there are insights to be gained from taking a systems view of our current patchwork of regulation and oversight”.
as is research conducted in certain jurisdictions (Newfoundland, for example, and Québec to a large extent). From a system perspective, the Standards have added a framework for standard operating procedures (SOPs) for institutions and REBs that review and conduct clinical trials with Health Canada regulated products. As such, the Standards, while adding a procedural layer to the *Food and Drugs Act* silo, do not provide (and are not intended to provide) a comprehensive national standard for human participant research protection programs.

In some provinces, efforts have already been made to create provincial governance frameworks comprised of clear rules, policies and procedures, and a designated authority. An increasing number of jurisdictions are developing similar provincial/territorial approaches. (For further discussion on this item, see Section 4.) The Standard might also serve as a governance and procedural framework in provinces/territories where similar frameworks or initiatives do not exist. Where efforts have already generated a governance framework, it may be necessary to generate notices of equivalency with the Standards. Time will tell if the Standards will play a more important role and fill a gap by serving as the basis of an accreditation system.

Overall however, the TCPS 2 and Standards have not filled the regulatory gap\(^4\), nor have they simplified the regulatory landscape.

### 3.1.2 Uninvolved research participants

With the notable exception of the provisions on research with First Nations, Inuit and Metis peoples, the TCPS2 does not have procedural requirements for including research participants\(^5\) in RPPP processes, other than, possibly, at the ethics review stage. As is discussed further in part 3.3, the Standards introduce requirements for consultation with research “subjects”\(^6\) as part of quality management activities, although there is no mention of precise activities that might be conducted. All in all, participant involvement remains marginal.

### 3.1.3 Still too much focus on REBs?

Despite the change from an approach based on the ethics review process to a research participant protection *program* (RPPP), research ethics still rely heavily on the REB. For certain processes (accountable structures, policy development, education, quality) research institutions are being tasked, at least officially by TCPS and the Standards. In practice, however, REB responsibilities continue to be interpreted broadly and may need reconsideration for reasons discussed elsewhere\(^7\). Practice (and research documented in the Report bibliography) demonstrates that there are continuing limits on what REBs can accomplish and some core responsibilities are still

\(^{4}\) As described in Hadkis 2011 at 450, quoting the Expert Committee for Human Participant Protection in Canada, *Moving Ahead Final Report 2008* (no longer accessible on website): “[there] are many gaps in the current [research governance] arrangements, including much unfunded research, some industry sponsored non-drug studies, some community based research, and some government or private sector research.”

\(^{5}\) McDonald, 2011, p. 45

\(^{6}\) The Standard refers to “subjects” as opposed to participants possibly to be consistent with the Food and Drugs Act and regulations.

\(^{7}\) Anderson et.al.2011
unrealized. A good example is the responsibility for continuing (or “on-going”) ethics review (Column 8.4), which generally continues to be a minimal paper review, plus the occasional “monitoring” programme (such as monitoring the recruitment or consent process.) This prompts the question: beyond reviewing and approving various reports during the course of research (annual, protocol amendment, adverse events etc.), to what extent do REBs have responsibly for implementing more active components of the time intensive activities required for continuous ethics review? The TCPS2 refers to continuing review as being a “collective responsibility”. As some elements of continuing review continue to be unmet, institutions might consider other options: The development of research ethics offices with qualified professional staff, including a quality management function, may serve to effectively redistribute tasks.

The Standard draws a distinction between “continuing” and “ongoing” review, both being REB responsibilities, and adding that the REB may seek independent “monitoring.” Given these three terms are often used in every day communications to refer to the same kind of activity, this distinction may introduce some confusion. Here, again, the REB is heavily tasked.

A redistribution of tasks might facilitate a shift in focus by REBs on compliance8, facilitating greater attention on broader issues, such as the outcomes of research in terms of publication, the social value of outcomes and supporting "ethical researchers."9

3.1.4 The goal of research ethics

The 1998 version of the TCPS focused on the goal of facilitating protection of research participants through the creation of a research ethics governance framework. In 2010, the focus of the TCPS2 was broadened to include “two main goals”: 1) providing necessary protection of participants; and 2) serving the legitimate requirements of research.10 The second goal clearly relates to supporting “ethical researchers”, not simply reducing research ethics to the step of REB approval.11 Some commentators contend that research ethics should also have as an “...overarching aim, the maintenance of trust between the research community and society as a whole.”12 In other words, the “ethical researcher” should work to build trust in participant-researcher relationships, rather than simply aiming to achieve REB approval. REB submission forms could prompt researchers to reflect on the necessary components of trust by asking questions, such as:

- What is my relationship to this person in this context?
- How might this context change over the course of the research project?
- What would be the resultant change in my relationship—especially as related to issues of power—to/with my participant(s)?

8 McDonald, 2011, p. 41
9 See Rivière p. 195: “how regulatory bodies such as research ethics boards can create an unproductive tension between receiving “ethics approval”, and being “an ethical researcher”. Also, McDonald, 2011 p. 45.
10 TCPS 2010, p. 11
11 “The narrow vision of research ethics as REB review, combined with the de facto limitations of the REB system, creates conditions ripe for institutional failure.” Anderson 2011, p. 13
12 Law Commission of Canada Report quoted in Anderson et al., 2011, p.12
o How, then, would I reinforce/reassure/reinstate the relationship of trust that I am developing with my participants?"\textsuperscript{13}

Developed in the social research context, the general thrust of these questions is certainly relevant to any field of research with humans. The extensive lists of elements to be considered in the ethics review process (table 5, column 5.3) do not touch the issue of trust and relationships, indicating potential for improvement.

### 3.1.5 Education

Education of REB members and researchers (Column 1.3), while supported in TCPS2 and the Standard, still lacks a structured approach in many jurisdictions. This may be because institutions (under the TCPS2) and REB Chairs (under the Standard) are tasked with providing or ensuring the provision of education programs. Training programs must also be comprehensive in order to best assist researchers and REBs. The TCPS 1998 tutorial has been completed by over 35,000 people. While it is not precisely clear what categories of individuals are taking the TCPS tutorial, at least one region has demonstrated increased uptake by researchers of existing ethics training programs after the introduction of a formal training requirement by the provincial funding agency.\textsuperscript{14}

This prompts the question of whether researchers ought to be required to follow minimal ethics training, who should develop such training, and how to evaluate its impact. Similarly, while localized offerings of training are welcome, given their critical role, some sort of certification for REB members and/or provision of a core curriculum would be useful for assessing knowledge and understanding. In addition, standardized education (or, at least, orientation initiatives) would facilitate opportunities for sharing and harmonizing best practices, especially for topics where discrepancies persist (for example, on placebo use.)\textsuperscript{15} How responsibilities should be split between federal and provincial governments, as well as between government and institutions, and between institutions, needs further discussion, especially with regard to scarce resources.

### 3.1.6 Links missing with scientific misconduct

The topics of scientific misconduct and the responsible conduct of research are completely absent in the TCPS2 and the Standard. While it is desirable to maintain a clear demarcation between the functions of ethics review and consideration of scientific integrity, this does not eliminate the need for RPPPs to consider how these functions fit together, or how related roles and responsibilities overlap. As Master has noted, while there is a persisting focus in Canada on ethics and governance of research involving humans, “[l]ittle attention, however, has been paid to the ethics and governance of RCR” (i.e., “responsible conduct of research.”) Many countries have developed

\textsuperscript{13} Rivière, 2011, p. 202-3.

\textsuperscript{14} Hirtle, 2012.

<http://ethique.msss.gouv.qc.ca/site/download.php?af249f5c1607a3a757c92bf527ba508a>

\textsuperscript{15} Sampson et al., 2011, p.75
research integrity governance systems. While Canada has made some headway in developing similar systems (including a Tri-council Panel on Responsible Conduct of Research (PRCR)), there is much room for improvement.”

3.1.7 Independent and competent REBs

Composition: As reported previously in 2007, requirements for REB composition are inconsistent, though not in direct conflict, across a number of key normative documents (i.e., TCPS, Div. V., GCP and some provincial regulations). The Standard adds another set of composition requirements that, again, are not in direct conflict, but just different enough to add complexity to this issue.

Competence: TCPS2 (art.6.5) and the Standard (4.3.2.5) are at odds with the Clinical trials chapter of TCPS (art. 11.1) in terms of the firmness of the requirement that REBs ensure expertise and competence by seeking external expertise for particular projects. Given how critical REB competence is for ensuring a fair evaluation of a project, as well as for ensuring participant protection, the use of “should” and “may” in TCPS art 6.5 and the Standard, is surprising. All the more so in the TCPS2 that goes to require additional expertise in the case of clinical trials.

Conflicts of interest of REB members: Hadkis provides a clear explanation of why REBs are most likely to be considered by the courts as being subject administrative law principles. Given the impact of a REB’s decisions on others (e.g., researchers, research teams, students, participants and institutions) the processes used by REBs are of critical importance and decisions must be, and must be perceived as, being fair. While judicial review might be a possible pursuit of unsatisfied researchers, the realm of administrative law also provides a wealth of procedural principles that can supplement research ethics normative documents. In light of this, Hadkis (2011 at 463) notes:

“The TCPS[2] does not contain a general test for determining whether an apparent conflict of interest exists on the part of REB members. Nonetheless, this instrument contains more direction on the issue of conflict of interest than the Clinical Trials Regulations, which are entirely silent on the matter, or the GCP Guidelines, which provide only scant directives. If administrative law applies to REBs, it can fill the void by furnishing the judicial definition of a reasonable apprehension of bias and a rich body of case law interpreting the rule against bias in a variety of decision-making contexts.”

The Standards direct institutions to develop local policies and instruct REB members to consult the REB Chairperson, but little substantive guidance is provided, let alone a general test. The point

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16 For example, Master suggests that a central body that researchers can turn to for advice that conducts educational activities and that might oversee investigations. “The development of a strong and publicly accountable Canadian research integrity system requires an all-encompassing approach including policy and procedures, best practices, education and outreach, institutional backing and research on research integrity.” See Z. Master, 2012.

17 Hadkis, 2011, 453

18 For a discussion about the use of « should » and « shall » see Hadkis, 2011, at 454

19 Hadkis, 2011 455 ff.
here is that, on the one hand, REB independence and impartiality is important. On the other hand, there are multiple kinds of situations that might lead to conflicts. The accompanying procedural gaps among RPPPs create the potential for allegations of bias and corresponding harms to public trust.

3.2 Need for tools to optimize implementation of policy requirements

Also on the topic of conflicts of interests, a recent Canadian survey of investigators demonstrates that clear criteria for reporting financial conflicts of interest, introduced early in the protocol development process, are effective:

“Full adherence to practices designed to promote the objectivity of research varied across trial stages and was low overall, particularly for industry funded trials. Adherence to preferred practices was highest when they were required by an external agent. Guidance introduced early in the trial process could alert investigators to preferred practices and encourage their incorporation into the study design.”20 [our emphasis]

Thus, broad requirements for self-reporting of conflicts of interests at the time of REB review (so part way through the life cycle of a research project) seems to be less effective than working towards an external reporting requirement introduced at earlier stages of the research. One team of researchers has proposed a checklist21 to help researchers report comprehensive information about financial conflicts of interest and to promote transparency at all stages of the research and publication process.

Rules and basic disclosure requirements for managing conflicts of interest (i.e., for researchers, REB members, or (more recently) institutions) have existed for some time (columns 2.1.4, 5.4, 6.3). However, to fully implement rules about financial conflicts of interest (which may be the easiest to identify), additional tools (in the case above a checklist to be filled out at several stages of the research) appear to be needed to fully realize lack of bias, independence and transparency. If used widely and developed for a greater breadth of stakeholders, such tools would be significant steps towards operationalizing the intent behind existing rules. This raises questions about how institutional conflict of interests (Column 2.1.4) will in practice be identified, eliminated, minimized, or otherwise managed by institutional mechanisms in place. Unfortunately, the Standard offers little guidance on how to achieve an efficient level of implementation.

Another example of a tool filling a gap (to some extent) is the exhaustive list of elements that fall under ethics review provided in the Standard (Column 5.3). Indeed, while the TCPS2 covers these ethical issues in detail, there is no basic template or guide for review. The ICH-GCP includes lists of items to consider, but these are specific to drug trials.

20 Rochon 2011 p.7
21 Rochon et al., 2010
Tools used to guide (as opposed to limit) the conduct and review of research facilitate the work of REBs and researchers in so far as they make expectations more concrete and provide a common minimal standard from which to build local practices.

### 3.3 Accountability and Transparency

Ongoing criticism of both RPPPs and the broader research ethics governance framework includes concerns about lack of transparency and of “ethically sound accountability mechanisms.” However, given the current model of delegated self-regulation (government delegates research institutions to self-regulate), addressing these concerns would require a massive overhaul, moving towards a geographically based ethics review system (e.g., such as the approach in Newfoundland and Labrador.) Given a complete overhaul of the federal governance framework is unlikely, other means for increasing accountability and transparency must be explored. Accreditation and increased quality management may provide appropriate alternatives.

While not new, of greater concern is the continued opacity surrounding cases of participants who are harmed or die. Very little is known about such incidents in private sector research. The public must rely on journalistic sources for these stories, as sadly, public sources offer very little information. As one author has stated, “[i]t’s equally difficult to obtain numbers from the public and private agencies that oversee human research subjects, such as research ethics boards (REBs) and Health Canada.” Given the importance of learning from mistakes, this continued lack of transparency is a significant gap.

The quality management provisions in the Standards specify at 4.6.6.1(c) that a program of continuous quality improvement should include “[a]ny feedback from investigators, sponsors, funders and research subjects.” (See Appendix B at 2.1.5.) Quality management review of the REB should also include at planned internals “[f]eedback from...public outreach to research subjects”, as noted at 4.6.2.1(d). While the kind of methods that should be used to obtain feedback from “subjects” is not specified, inclusion of participant feedback serves to acknowledge the importance of considering participants experience (good or bad) for ensuring quality of ethics processes. Implementation of quality programs, with an emphasis on transparency, might begin to address concerns. (For more on the quality management provisions in the Standards, see section 3.5 below.)

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22 McDonald et al., 2011
23 Schuman, 2010
24 Such as those related to harmed participants and those expressed by McDonald et al., 2011, p. 43 “REB review processes lack transparency. REB operations and attendant institutional participant protection measures are cloaked in secrecy, which means there is little in the way of inter-institutional learning from mishaps [or for that matter, successes] with the potential concomitant erosion of public confidence.”
3.4 Variability in the how the concept of “confidentiality” is used

For the 2014 Report at element 1, Column 1.4 was previous listed as “Communication & Transparency.” This has been expanded to “Communication & Transparency/Confidentiality.” As a component of the review and conduct of specific protocols, “confidentiality” refers to the duty not to disclose identifiable information about participants outside of study activities. As a component of processes requirements, the Standard addresses the necessity of maintaining confidentiality by REB members, institutional staff and sponsors, as well as confidentiality of other kinds of information, such as the proceedings of REB meetings and discussions. Finally (and not previously mentioned in any documents reviewed for the Comparative Analysis to date), clinical trial sponsors may require that corporate information found in protocols be kept secret. The Standard also emphasizes the importance of transparency with regard to the content and language in SOPs to ensure actual and perceived fairness by researchers. REBs will need to be careful as they navigate the fine line between keeping the content of deliberations confidential, while striving for transparency and communication with researchers and other REBs.

As suggested in part 4 of this report, including a review of recent changes to some provincial access-to-information (ATI) legislation would indicate whether or not documents such as the minutes of REB meetings and others records about decisions made might be impacted by ATI requests. Given recent interpretations in the TCPS2 provisions on whether or not minutes ought to be made public25, guidance to REBs might conflict with provincial legislation.

In light of the recent decisions from the Québec case Parent v. Q, that involves criminal proceedings against Magnotta, there is reason to be concerned over the absence of mechanisms like confidentiality certificates for protection of highly sensitive participant data when a search warrant has been issued. For the first time in the Canadian context, the court recognizes a case-by-case research-participant confidentiality privilege (which is a higher form of confidentiality in common law.) Without going into too much detail, it is noteworthy that the court upheld the confidentiality of the research participant’s personal information that had been communicated with a promise of strict confidentiality. Also noteworthy, are the reasons given by the Court to quash the warrant: after looking in detail at the recruitment and consent documents as well a number of other elements, the judge asked to review the research data and came to the conclusion that its relevance was “minimal at most and marginal.” Thus, the court decision is intimately related to the contents of the interview and to the charges laid. This could translate into a lack of predictability regarding any assurances made to future participants by researchers about confidentiality.

25 From pre website interpretations: 6. Should institutions make REB minutes publicly available? (July 2012)
- There is no general requirement in TCPS 2 regarding public accessibility of REB minutes. What TCPS 2 advises in the application of Article 6.17 is that files, minutes and other relevant documentation must be accessible to the authorized representatives of the institution, researchers, sponsors and funders under certain circumstances “when necessary to assist internal and external audits, or research monitoring, and to facilitate reconsideration or appeals.” (Application of Article 6.17).
- While not specific to public sharing of minutes, it should be noted that guidance in TCPS 2 encourages institutions' transparency to demonstrate their accountability while maintaining researchers' confidentiality (see Application of Article 6.1).
Given the potential risks to participants and to research, the TCPS2 should include guidance on how institutions, researchers and REBs can work towards ensuring that the “Wigmore” criteria are met, as applied in this case. If projects that propose to collect highly sensitive personal information can at least be structured to meet the first three criteria, then they will qualify to benefit of judicial review that assures that only personal information relevant to a trial is disclosed. The lack of guidance on how to meet the Wigmore criteria is a significant gap.

3.5 Ethics and quality management of RPPP

Since 2007, some authors have described ongoing issues related to the absence of requirements for robust quality management of ethics review processes, including quality assurance and quality improvement. A notable addition to the process requirements landscape is part 4.6 of the Standards, “Quality Management.” While “quality assessment” was included in the 2007 Report (Column 8.7), this was in reference to ongoing review by a REB and auditing individual research projects for compliance. The quality management section in the Standard is not about auditing projects, but about quality of the RPPP, REB activities and related processes. For this reason, the quality management requirements in the Standard appear in a different place in the Appendix B tables of the 2014 Report; see column 2.1.5, “Evaluation/Quality Management.” Note that while the Standard document is specific to ethics review processes for clinical trials, the general approach to ethics quality processes could extend to processes for any research with human participants.

In keeping with established frameworks for quality management, the concept of “quality management” in the Standard part 4.6 includes:

i) requirements for review and evaluation of activities and associated process documents (sometimes conceptualized as quality assurance);

ii) requirements for conducting performance measurement and control of deviations (quality control); and

iii) requirements for continuous improvement, including obtaining feedback from investigators, sponsors, funders and research subjects to inform corrective and preventative actions (quality improvement).

While the descriptions of the components of “quality management” in the Standard do not, in our view, correspond precisely with concepts as found with some established philosophies and

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26 Shuman, M., Research Participant confidentiality now a formal concept in Canadian Law, CMAJ, February 3, 2014: “Wigmore criteria, a four-step analysis to determine if a particular communication should be protected against disclosure. The case hinged on whether the public interest in obtaining the “Jimmy” interview for the investigation and suppression of crime outweighed the interest in what Justice Bourque described as “the free flow of accurate and pertinent information,” which could dry up without a reliable promise of confidentiality. She broke the seal and reviewed the interview transcript privately, but did not share its contents, writing that its relevancy to the charges against Magnotta or to a “not criminally responsible” defence was “minimal at most and marginal.” Bourque quashed the search warrant, concluding that “the Confidential Interview is covered by the researcher-participant confidentiality privilege and…it should not be disclosed.”

27 McDonald et al., 2011, p. 39.

28 J Evans & Lindsay, 2014.
theories of quality management\textsuperscript{29}, part 4.6 is a significant gesture to the importance of managing for quality in RPPPs. The need for inclusion of this component has been acknowledged in the literature; for example, McDonald et al (2011) have noted that while some quality processes, practices and research initiatives are in place within some RPPPs, current weaknesses rest in the lack of independent and expert quality assurance and quality improvement for all parts of the ethics review lifecycle, the lack of systemic implementation of quality review activities, as well as the lack of ethical performance indicators and no real feedback from participants. While it does not specify what the substance of the various activities and procedures would be (i.e., it does not provide detailed criteria for conducting an evaluation), part 4.6 includes detailed lists of the kinds of activities that would be part of a quality management program and calls for documented procedures. For example, a quality control component would include collection and analysis of incident data using appropriate metrics that would serve to measure the efficacy of the ethics review processes that result in more appropriate requirements for researchers.\textsuperscript{30} This would inform quality improvement activities, for example, enhancing the efficiency and consistency of REB approval processes through feedback from the quality control activities, as well as through consultation with various stakeholders (e.g., research coordinators, investigators and members of the lay public.)\textsuperscript{31}

The Standard acknowledges a range of possible options regarding the question of which department or program within an institution would best oversee and implement a quality management program, noting at 4.6.1.1 that “...quality management processes may be the responsibility of the REB Chair and REB administrative staff or may be the responsibility of a distinct entity within the organization.” However, some current practices suggest that even compliance audits of researchers, if conducted by the REB, tend to reveal the need for correction of something related to an REB procedure.\textsuperscript{32} If the goal of the quality management program (as set out at 4.6 of the Standard) is to review the activities and processes of the REB, and the REB itself undertakes the review, then such REB “self assessment” presents a risk of conflict of interest. As an example, the current trend in some US institutions is to conduct quality management programs (both of research projects and of IRB activities and procedures) in parallel and cooperatively with, but separate from, the IRB.\textsuperscript{33} Some Canadian institutions also have parallel programs for quality

\textsuperscript{29} For example, within the theory of quality management espoused by the quality pioneer Joseph Juran, “quality improvement” involves achieving “unprecedented levels of performance”, i.e., it is not limited to implementing corrective and preventative actions, but extends to aspirations of excellence. Consistent with other quality gurus, the highest goals for improvement should be ongoing and part of the culture of an organization. See Evans & Lindsay, 2014, p 61.

\textsuperscript{30} The importance of collection and analysis of incident data as part of quality activities that would serve to measure the efficacy of the ethics review processes and result in requirements for researchers is discussed by Mueller and Furedy: “If there is no evidence supporting the effectiveness of the review process, we really should ask now much ineffective regulation we are willing to impose on researchers...identifying alleged problems does not indicate that the ethics review process is successful at avoiding incidents (real or imagined) in the experimental setting.” See Mueller et al., 2013. This is echoed by Grady: “Without evaluative date, it is unclear to what extent IRBs achieve their goal of enhancing appropriate clinical research. This lack of data is complicated by the reality of no agreed-on metrics or outcome measures for evaluating IRB effectiveness.” See GRADY 2010.

\textsuperscript{31} See, for example, the results of the study conducted by K. Lutz et al., 2012, which focused on the need for streamlining review processes to enhance efficiencies in an international clinical trial.

\textsuperscript{32} For example, if a for-cause audit is conducted in response to a complaint by a participant about a new issue never considered by the REB before, the outcomes of the audit might indicate that the new issue needs to be incorporated into REB submission forms or checklists. If the audit is conducted by the REB itself, given the outcomes are about REB processes, such “self audit” would at least be perceived as a conflict of interest.

\textsuperscript{33} Reference to agenda from the PRIM&R/AER conference; See the ‘19’ series in programme https://www.prirm.org/aer13/
management of research in place. While these programs are focused on quality of research activities (rather than REB processes), they appear from their online descriptions to be functions that are separate from ethics review and, notably, emphasize the importance of transparency and accountability for ethics oversight processes within the institution.\textsuperscript{34}

The TCPS2 is virtually silent on the need for quality management of RPPP.

### 3.6 Review of Multi-site research

The TCPS2 allows institutions to use different models for ethics review as long as formal agreements between institutions are signed. It offers options, as opposed to a solution, which is understandable given the need to meet the needs of different kinds of research conducted in different jurisdictions. It also demonstrates, in our view, that any system to streamline the review of multi-site research will need to emerge province-by-province. As such, Canada is still a long way away from a national streamlined approach.

In contrast, the Standard implements the “REB of Record” concept by which various organizations involved in a multi-site clinical trial could enter into an agreement and thereby delegate a single REB to conduct initial and ongoing review for all sites. This is similar in some respects to the Ontario Cancer Research Ethics Board (OCREB) model in Ontario and to the Québec model. However, many elements will need to be addressed in the “agreements”, for example: how ongoing review will actually occur; who will cover costs; how local organisations will give their final agreement to participate; and what to do if certain aspects of the trial need be modified in order to accommodate local contexts. In addition, signed agreements are important tools for addressing underlying concerns over legal liability that remains with institutions that host the research, even if a central REB reviewed and approved a protocol. Such agreements must follow established templates in order to avoid introducing variations, which in turn can increase delays and make it difficult to conduct research in an already highly competitive environment.

Recent studies\textsuperscript{35} continue to document the cost, inefficiencies, delays and inconsistencies generated by the lack of a centralized ethics review mechanism for the review of multi-site research. Consensus is emerging within the literature about the persistent difficulties surrounding streamlining of ethics review in Canada, as well as the need to develop further procedural elements to support efficient ethics processes. Not surprisingly, these elements include accreditation, standards for education of REB members and researchers, and discussion about the underlying issue of institutional liability. These elements are not addressed in the TCPS2, or the Standard.

\textsuperscript{34} See, for example, the website of the University of Manitoba’s Research Quality Management, as described on its own web page: http://umanitoba.ca/research/orec/ga/qm.html (accessed online February 28, 2014.) As stated on this web page, the University is of the view that it is an obligation of the institution “...to establish processes of oversight for the conduct of human research within its institution” and that “[t]hese processes must be both transparent and accountable while they facilitate and support important and useful research.”

\textsuperscript{35} Ezzat et al. 2011; Caulfield et al 2011; Master et al, 2011; Saginur, et al, 2009; McDonald, et al. 2011
3.7 New elements

While there are several novel elements found in the TCPS2 and the Standard (institutional conflicts of interest and quality management among them), two new elements stand out and address specific contexts with interesting processes (and so are worth mentioning in this section.)

3.7.1 Ethics review during public emergencies

The TCPS2 delegates to institutions the task of developing local policies for the review of research during publicly declared emergencies. While allowing local issues to be addressed, the absence of a model framework may lead to variations across the country. As the goal is to increase flexibility in the process of ethics review to meet emergency situations, variability may be inevitable.

Of note is a framework proposed by a group of researchers for conducting emergency ethics review and that “explicitly combines increased diligence (similar to that of special scrutiny) with enhanced procedural flexibility (consistent with expedited review) in a manner that is proportionate to the perceived risks and specific circumstances associated with the research protocol.” Given the novelty of these procedures, it would be important to build into any framework for flexible review an evaluation component (should this new procedure ever be tested.)

3.7.2 Research with First Nations, Inuit and Metis peoples

The importance of considering themes specific to indigenous peoples is apparent in the TCPS2 from the addition of Chapter 9, “Research Involving the First Nations, Inuit and Metis Peoples of Canada.” Requirements address, for example, the need for engagement of communities to appropriate degrees and within various processes (e.g., obtaining input from communities and advice from elders during the research planning stage to ensure respect at all stages of the research process and community interests in the resulting findings/data; including community representation during ethics review.) While not as extensive as Chapter 9, the requirements in the Standards about involvement of First Nations, Inuit and Metis peoples is consistent with some of the themes in the TCPS2, specifically with regard to including representatives on the REB and where a protocol will require consideration of significant interests or concerns of First Nations, Inuit and Metis communities.

As noted in Appendix A and the creation of a new sub-element at section 9.2, requirements specific to First Nations, Inuit and Metis peoples are new additions to previous frameworks, and highly significant, given the cultural interests that they work to respect. However, from our experience of working with First Nations researchers, we are aware that considerable discontent exist within some First Nations communities related to Chapter 9 of the TCPS2 in particular. This is reflected, for example, in the “OCAP™ principles” (“ownership, control, access and possession”) espoused and
trademarked by the First Nations Information Governance Centre (FNIGC).\textsuperscript{37} While the principles are mentioned in Chapter 9, it can be argued that they do not provide the main foundation of the approach set out and, in particular, that they do not provide the degree of guarantee or a sufficient degree of control of review processes that might ensure that the outcomes not only benefit First Nations, but constitute ownership in the process as well.

In addition, we are aware that the process of consulting with First Nations communities (as described in the Standard, for example) requires attention to details that might not be significant for consultations with other populations. For example, respectful consultation can require extensive engagement of communities and elders. As well, respect may require ensuring sufficient time for consultation activities to evolve. As such, process requirements should anticipate time horizons that ensure respectful engagement.

It is possible that some First Nations organizations have elaborated further on related process requirements and that it will be appropriate to review them for the purposes of the continuing updates to the Comparative Analysis.

4. RECOMMENDATIONS, CONCLUSIONS AND NEXT STEPS

The main recommendation of this 2014 Report is, of course, that the work towards updating the Comparative Analysis be completed to ensure a completeness, comprehensiveness and accuracy throughout.

In addition, we offer the following concluding remarks as part of a plan for moving forward, as well as “food for thought.”

- **Trend towards more, not less**

  In 2014, the normative framework relevant to research involving humans has more, not less, applicable documents and rules and procedures. This results in a continued complex patchwork of normative documents.

- **Contributions from academia but why not from ethics practitioners as well?**

  Academic researchers are conducting research on the ethics review function, some of which is practice-based and leads to a better understanding of the concrete effect of requirements and procedures. Academics have also contributed practical tools, such as checklists (on financial conflict of interest) and model frameworks (public emergencies.) Such tools should be made accessible so that they can be tested in the field of research ethics, accompanied by “feedback loops” in order to improve any shortcomings (consistent with quality improvement activities.)

These academic endeavours should continue to be supported as a means of evaluating the impact of the normative framework and providing tools to implement policies. Additionally, ethics

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\textsuperscript{37} http://fnigc.ca/ocap.html (accessed online March 3, 2014.)
practitioners should be encouraged and supported to conduct more practice-based research and
develop tools, thereby making use of their specialized expertise and improving towards systems
overall. For example, institutions are tasked with developing a number of policies and SOPs. Could
they also provide models of the various tools, SOPs, checklists etc., needed to operate their own
RPPP? Quality management tools could also be shared to everyone’s advantage. Looking into best
practices and tools offered by CAREB might fill an important gap in this Comparative analysis.

• **Controversy: Placebo trials**
  The 2007 Comparative Analysis noted that the lack of consistent criteria regarding the
acceptability of placebo trials. This left researchers and REBs with mixed guidance about how best
to proceed with review of placebo trials. The issue would receive much-deserved attention via
comparison of the ICH-GCP, TCPS2 and the 2013 amendments to the Declaration of Helsinki, when
the comprehensive 2014 update of the Comparative Analysis is completed.

• **Minimal risk standard**
  The minimal risk standard is used in many areas of ethics review as a critical threshold to
determine, for example, the level of initial and continuing ethics review, or again, whether
incompetent participants may be recruited. It would be important to review the how the minimal
risk standard is used across all documents (i.e., add a new element to the appendices) in order to
accurately assess if this standard is consistently and appropriately used to guide review
procedures.

• **Obligation unfulfilled: Safety reporting ADR, SAEs etc.**
  Adverse event reporting and review of adverse event reports is a critical element of ethics review
(at least, in clinical trials) for ensuring continued safety of participants. Nevertheless, concerns
persist regarding management of SAEs post-reporting and in relation to legal liability, and the
tendency for such concern to trump concerns over ensuring participant safety. As stated in one
source:

“\[To reduce legal liability due to a failure to warn, sponsors pass on to REBs all reports of\}
\[adverse events no matter how trivial or unrelated to the pharmaceutical being\}
\[tested. REBs are then forced to devote scarce resources to figuring out whether and\}
\[where there is a needle of danger in the haystack of reports.\]”\(^{38}\)

Various bodies are attempting to address this issue (including the US FDA and CAREB, for
example.) Hopefully, researchers that conduct clinical trials and the REBs that review those
studies understand how to best to protect participants. However, it is critical that a clear picture of
evolving reporting requirements, as well as any effective practices, be collated and understood.

• **Access to Information**
  Since 2007, changes have been made to access to information (“ATI”) legislation in many
provinces. For example, on January 1, 2012, Ontario hospitals became subject to the provincial

\(^{38}\) McDonald p. 43
Freedom of Information and Protection of Privacy Act ("FIPPA"). This represented a significant change for hospitals and their stakeholders regarding hospitals’ obligations to disclose records. Indeed, the intent was to help increase the transparency and accountability of the hospital system. The change aligns Ontario with many other Canadian provinces (including British Columbia, Alberta, Saskatchewan, Manitoba and Quebec), where public hospitals (or regional health authorities) are already subject to ATI laws. One core purpose of Ontario’s FIPPA is to provide a right of access to records under the custody or control of institutions. Whether or not “records” might include proceedings of hospital-based REBs cannot be known without including a review of FIPPA and comparable laws in other provinces/territories as part of a thorough review of the Comparative Analysis. Insofar as REB proceedings and associated documents might be included in the definition of “records”, there would likely be associated impacts on REB process requirements.

- Next Steps:
The following documents are offered as a preliminary list of documents that should be explored in future versions of this Comparative analysis. (Note that detailed research will be required for a comprehensive list.)

- Verify for updates to Health Canada documents such as the Compliance and Enforcement Policy, 2005
- WHO Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants, (WHO Standards) 2011,
- The Declaration of Helsinki, 2013
- Quebec Civil Code, Loi sur les Services de santé et des Services sociaux
- Clinical Trials Ontario– REB qualification program
- Ontario Cancer Research Ethics Board
- Alberta Research and Innovation Act and the Alberta Research and Innovation Regulation
- BC Ethics Harmonization initiative
- International publishers requirements
- US FDA

These suggestions are provided as an indication that the field is evolving, quickly. And, mastering the maze of regulations requires ongoing commitment by the many stakeholders involved.
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