Summary:
Draft Preliminary Recommendations
Of the CCTCC REB Accreditation Working Group

INITIAL DRAFT: **NOT APPROVED O**R COMMENTED ON BY THE FULL ACCREDITATION WORKING GROUP MEMBERSHIP

1 PREAMBLE

The responsibility for human research protections lies with the Canadian government (including Health Canada), then granting councils, the institutions that receive grant funding from the councils, pharmaceutical companies that sponsor clinical trials, the researchers who conduct research involving human participants, the private and institutional Research Ethics Boards (REBs) that review such research and also with the public. The Canadian Clinical Trials Coordinating Centre (CCTCC) REB Accreditation working group (hereafter the "working group") believes that all of these stakeholders need to be integrally involved in supporting efforts to enhance quality, efficiency and effectiveness of research involving human participants. The recommendations outlined in this document are only a first step towards development of a more robust national system of human research protection.

2 MANDATE AND TERMS OF REFERENCE

The CCTCC working group on developing a pan-Canadian accreditation system for REBs that review clinical trials was established in April 2015. The Terms of Reference stipulated that the working group was to investigate the critical questions involved in the development of strategies to improve ethics review efficiency [The 2012 Clinical Trial Summit Action Plan], strategies to standardize the research ethics review process and for either the accreditation of REBs [The 2012 report of the Standing Senate Committee on Social Affairs, Science and Technology, *Canada's Clinical Trial* Infrastructure] or for another approach to the development of a system for the evaluation and qualification of REBs. [The 2013 Strategy on Patient-Oriented Research (SPOR) External Ethics Advisory Committee report]

The working group created an interim report and with funding from the CCTCC retained a consultant to assist it in its deliberations and recommendations. The initial recommendations that follow are informed by that information, but not limited by it. They are the opinions of the working group which represents a diversity of expertise within the field of research and research ethics. The recommendations are initial recommendations only. The working group's final recommendations will

necessarily be informed by the feedback received from a broad call for comments from the REB, researcher and participant communities as is suggested in the first recommendation (point 3, item A).

Following each recommendation are suggestions concerning possible parties that may assist with implementing each of these recommendations. There are likely other stakeholders and interested parties who should be involved, and it is hoped that who these other parties should be will become apparent from the feedback received from the call for comments.

Action on recommendations C through J necessarily follows from execution of recommendations A and B (see point 3).

3 Initial Recommendations

A. Engage in discussion with the REB, researcher and ultimately the participant communities to obtain input on the working group recommendations and next steps. [recommendation directed to Canadian Association of Research Ethics Boards (CAREB), Panel on Research Ethics (PRE), Network of Networks (N2), and CCTCC]
B. Establish a national strategic leadership forum as an initial step toward development of a governance model for human research protections in Canada. The leadership forum would be modelled after the US Secretary's Advisory Committee on Human Research Protections (SACHRP). It would be funded by and accountable to the key stakeholders involved in the area of human research protections. Potential key stakeholders are suggested in this document. The final determination of which organizations would participate in the proposed external governance body, what the scope of authority of the leadership forum would be, and criteria for membership in it must be informed by the call for comments. [recommendation directed to CCTCC, CAREB, PRE]
C. Commence discussions with potential partners for the development of a mandatory registry of REBs. The Registry would potentially be managed by the PRE with collaboration and input from the CAREB and the CCTCC. Registration would provide access to a suite of education and training opportunities for example via CAREB, PRE and N2/Collaborative Institutional Training Initiative (CITI). [recommendation directed to CCTCC, PRE, CAREB and Health Canada]
D. A meeting of key stakeholders (including the Canadian Institutes of Health Research – CIHR –, Health Canada, CAREB, PRE and representatives from the provincial harmonization initiatives) should be convened to discuss the potential imposition of a mandated equivalency requirement for all REBs that review and approve regulated clinical trials. Equivalency would be against established standards such as the Association of Accredited Human Research Protections (AAHRPP) accreditation, Clinical Trials Ontario (CTO) qualification, or Ministère de la Santé et des Services sociaux (MSSS) designation standards. [recommendation directed to CCTCC]

E. Investigate and report on the national and provincial legislative barriers to pan-Canadian acceptance of a review by another Canadian or a central REB. This would include investigating the private REB model to determine how it has overcome these issues. [recommendation directed to CCTCC, PRE, Health Canada]
F. Investigate and report on the institutional liability issues involved with pan-Canadian acceptance of a review by another Canadian or a central REB, including recommended solutions (e.g. appropriate legal agreements, shared insurers, etc. [recommendation directed to CCTCC, PRE, Health Canada]
G. Investigate the feasibility of developing more formalized requirements and processes for sharing and/or posting of reviews of the same or similar studies, including the development of a precedent database. [recommendation directed to CAREB, PRE, N2, representatives from the provincial harmonization initiatives]
H. Undertake a prioritization exercise to identify the top education / training priorities for research ethics boards. [recommendation directed to CAREB, PRE, N2]
I. Facilitate awareness of existing efforts in the area of REB improvement, the 2013 Streamlining Research Ethics Review (SHRER) Committee report and its appendices should be more broadly disseminated. [recommendation directed to CIHR, SPOR]
J. Explore process measures to improve efficiency in clinical trial review investigations concerning the feasibility of a national on-line system for multi-centre reviews. [recommendation directed to CCTCC]

4. Rationale For Recommendations

A. The Importance of Engagement and Meaningful Consultation

Crucial to the success of any efforts to assess and enhance the quality, and efficiency and effectiveness of research ethics reviews in Canada is the need for grassroots consultation and building a system or systems from the ground up. This includes the need for sufficient outreach to the research ethics community. This theme emerged from the consultant's report as being a determining factor for achieving success in both harmonization / centralization efforts and for the uptake of any accreditation system. Systems such as the Ontario Cancer Research Ethics Board's (OCREB's) and CTO's, built on meaningful community consultations are better able to address organizational and other requirements and ultimately are easier to operationalize. Without purposeful, early and continuous engagement with the impacted REB community, including soliciting and considering feedback on any proposals for any form or process of assessment, the necessary credibility required for buy-in and uptake of the system will not be created and the risk of failure will be significant. The need for engagement and consultation is not restricted to the research ethics community. Input from researchers as well as research

participants should also be solicited, particularly as work on developing a more robust system for the broader spectrum of the protection of human research participants is undertaken.

The engagement of stakeholders around topics such as research and healthcare can be justified on a number of grounds. Firstly, legitimacy and fairness demand that when research is funded by public funds, such as is the case with much of the health research in Canada, the public should be involved. Equally, fairness requires that those who will be most affected by the proposed change should be given a voice in the discussion. Greater involvement of the populations involved is also in-keeping with democratic principles [1], may provide greater support for the decisions made (assuming they are in-keeping with the expressed views), and could potentially lead to increased trust in the decision-makers and decision-making process. Finally, the involvement of the key stakeholders (including the public) allows for a wider range of perspectives that can lead to improved decisions [2]. Moreover, a failure to engage with relevant stakeholders can have negative consequences. Controversies surrounding genetically modified crops in Europe [3] and the marketing of nutrigenomics-based dietary advice in the UK [4] illustrate the 'setbacks and uncertainties' that can arise where there is a disconnect between innovation and social acceptance [5].

B. The Need for a National Strategic Leadership Forum

Human research protections and the subset of those protections that represents research ethics review in Canada lack a clearly defined governance model and appropriate resourcing. Despite previous proposals over the past decade efforts to establish a national program of assessment of human research protections in Canada have remained at a standstill. The two most significant reasons why past efforts have failed relate to lack of formal leadership and lack of resources, in particular, funding and support. There is a need for identified leadership as there is no clear authority that would either undertake the required consultative work (see Point 3, item A above) or provide the necessary practical support for the implementation of any proposed assessment model.

The US and UK systems while markedly different in both model and scope, have each had the support and endorsement of either a combined group of impacted stakeholder organizations (AAHRPP - US) or the national Health Research Authority (HRA - UK). The Institutional Review Boards (IRBs) accreditation program in the US is a part of an over-all human research protections framework that includes the Common Rule and the Office of Human Research Protections (OHRP) as well as SACHRP. SACHRP is a legislated committee that is responsible for advising the Secretary for Health and Humans Services on matters related to human research protections. When discussions pertaining to accreditation were occurring in the US, SACHRP established an accreditation sub-committee. In the current context of the discussions pertaining to the Notice of Proposed Rulemaking (NPRM), they have established a sub-committee on the NPRM.

There is historical support in Canada for establishing a strategic national leadership forum. In February 2013 the SHRER Committee concluded that a national strategic leadership forum should be created to:

- Facilitate communications between the various streamlining and harmonization initiatives
- Provide strategic insight into opportunities for national collaborations; and
- Identify potential groups to take responsibility for moving forward on the SHRER Committee recommendations.

The SHRER Committee recommendations were not taken forward in 2013. The current working group is making essentially the same recommendations again in 2016. The working group believes that if the recommendations are not implemented this time, this working group's report is destined to become a new tab in the binder of the next accreditation working group. Most significantly such a failure will signal a lack of official support for a more robust system of human research protections in Canada. At the very least, this failure to act will negatively impact trust in the research ethics community regarding future endeavors.

The working group is not recommending the creation of a separate institution or organization that would serve as the governing body for human research protections in Canada. Rather it is suggesting that a strategic leadership forum with varied (and changing) representation from across the country with local, provincial, regional and national interests in research ethics should be invited to participate in the forum. These key leaders should be funded to meet at least quarterly and otherwise as needed to provide strategic advice, direction related to national centralization and harmonization initiatives as well as accreditation and registration recommendations, and ultimately a governance model for human research protections in Canada.

The working group suggests that the leadership forum should be funded by and accountable to an external advisory board, made up of representatives from: The PRE, Health Canada, the Tri-Councils [CIHR, Natural Sciences and Engineering Research Council of Canada (NSERC), Social Sciences and Humanities Research Council of Canada (SSHRC)], Innovative Medicines Canada (IMC), CAREB, HealthCare*CAN*, NAPHRO and most importantly Innovation, Science and Economic Development Canada (ISED).

Enhancing the quality, efficiency and effectiveness of research ethics review and human research protections in Canada is directly linked to both economic and health and wellness benefits for Canada. The working group notes that one stakeholder who has not been significantly involved at the Canadian national table in these discussions is ISED. It is worth noting that Ontario's initiatives (CTO and OCREB), which arguably have achieved the most success in harmonization and centralization of research ethics processes, have the support of the provincial counterpart, i.e. Ontario's Ministry of Research and Innovation (MIT). Significantly, they also have the largest amount of dedicated funding for their initiatives.

C. The Need for a Registry of Research Ethics Boards in Canada

In its interim report of September 2015, the working group recommended that a registry of research ethics boards operating in Canada be developed. Discussions were held with CAREB and the CCTCC. CAREB is not resourced to develop such a tool at this point in time. In order to implement the recommendations of this report concerning a systems of assessment, education, and communications, it is necessary to know which organizations in Canada have authorized research ethics boards, which private corporations operate research ethics boards, and which of these review and approve sponsored clinical trials. In the US, the Federal Wide Assurance registry system for federally authorized IRBs is maintained and operated by the OHRP. The system is now merged with the US Food & Drug Administration requirements. The Canadian counterpart of OHRP is the PRE. Accordingly, the working group recommends that the PRE commence consultations with CAREB, Health Canada, CCTCC and other key stakeholders (e.g. N2) concerning the development and implementation of a mandatory registration mechanism. A positive incentive for such registration would be the provision of a suite of training and educational materials (see point 3, item H below). Careful consideration needs to be given to what information / data needs to be collected in the registry, as well as how to ensure that there is an effective mechanism for ensuring that the registry is kept up to date.

D. The Possible Implementation of an Equivalency Requirement for REBs that review and approve regulated Clinical Trials.

REBs that review regulated clinical trials are subject to numerous provincial, national and international regulations and guidelines. In Canada, very few if any REBs review only regulated clinical trials. While the need to ensure quality, consistency and efficiency of REB reviews extends to all research ethics boards, the most pressing requirement from a national economic and regulatory perspective is to ensure that those REBs that review regulated clinical trials meet common standards. There are operational standards such as the International Conference on Harmonization: Good Clinical Practice: Consolidated Guidelines (ICH-GCPs), the Canadian General Standards Board (CGSB) Standard and the US regulatory requirements that can be referenced, but there is no process in place to ensure that these applicable standards, guidelines and regulations are being applied in similar ways across REBs or between jurisdictions. The working group recommends that any move to require REBs that review and approve regulated clinical trials, to meet existing provincially or internationally developed qualifications standards be investigated and discussed by all key stakeholders, including those organizations and institutions that support REBs that review regulated clinical trials, representatives from the provincial initiatives, CCTCC, Health Canada and IMC. The working group believes, and it is supported by the data from the consultant's report, that there is no need to reinvent the wheel when it comes to developing an assessment system for REBs to review regulated clinical trials. Consideration should be given to utilizing or adopting existing standards. This includes the AAHRPP accreditation standards that most

privately operating REBs in Canada adhere to, the CTO qualifications standards, and the MSSS designation standards. REBs would not necessarily have to become AAHRPP, CTO or MSSS "qualified" but they would be required to demonstrate equivalency in some verifiable way. Given the legislative and/or liability issues that were noted during the consultant's discussions (see below) this may be a pragmatic approach that recognizes and builds on the work conducted by the provinces, while working toward the national standards that a pan-Canadian assessment system might be seen to provide.

Whatever approach is ultimately determined the working group strongly advocates that this be an evidence-informed process. Such a process will, therefore, require additional work to be undertaken to identify and develop appropriate tools or measures of evaluation in order to assess the benefits or improvements gained through any changes to the REB landscape.

E. Investigating the Legislative Barriers to pan-Canadian REB acceptance of a review by another Canadian or a central REB.

Streamlining and harmonization initiatives are being implemented in most Canadian provinces. There is no national organization facilitating cross-communication between those initiatives, and although there are some disease specific initiatives working on the feasibility of a single national review, there is no organization that is looking at the issue from the perspective of sponsored clinical trials. The US NPRM proposes the requirement for a single IRB review of studies conducted at multiple US sites and some US sponsors (notably the National Institute of Health – NIH) are currently requiring single IRB (within the US) review of multi-site studies that they fund. The US Federal and State legislative landscape with respect to IRB review is considerably more complex than Canada's. There are thousands of IRBs in the US, compared to hundreds in Canada. Despite initiatives such as the Canadian Cancer Clinical Trial Network (3CTN) ethics working group and other investigations into the feasibility of a single national REB for pan-Canadian studies, the conclusion consistently reached is that a single REB approach in Canada is problematic and not feasible. One of the reasons consistently cited as a barrier to pan-Canadian acceptance of another (extra-provincial) REB review is provincial legislation, most specifically, provincial privacy legislation. For instance, the health information legislation in Alberta requires that research involving the health information of residents of Alberta be reviewed and approved by a designated Albertan REB and that reports of their decisions are reported to the Alberta privacy commissioner. Legislation can be amended and repealed. If the goal of a single Canadian REB review of a pan-Canadian study is important for national economic reasons, a formal legal review of all of the legislative barriers including current provincial privacy laws should be undertaken, with the aim of recommending possible solutions for overcoming those barriers, either through legal agreements or legislative change.

The private REBs operating in Canada, have overcome some (but not all) of these challenges. They have developed systems and processes that have operationalized an initial review for a lead site, followed by approvals of additional sites with the secondary review focusing upon local site issues and local PI

qualifications. The feasibility of public institutions adopting the private REB model for studies that are pan-Canadian in nature, should be investigated, including the operational aspects as well as leadership and resources.

F. Investigate and report on the institutional liability issues involved with pan-Canadian acceptance of a review by another Canadian or Central REB

Despite statements contained within the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2:2014), and the existence of a report commissioned by Health Canada the public institutional REB community continues to believe that institutional liability issues are a significant barrier to non-local (external) REB review of studies conducted at their respective institutions. These concerns are being expressed by both the academic and the health authority REB communities. The working group recommends that a formal investigation of the institutional liability issues related to non-local (external) REB review is undertaken, with an aim to recommend various options for overcoming those issues, including, for example, appropriate individual or blanket / master agreements, acknowledgement of shared insurers etc. The results of this investigation should be made public on research ethics related web-sites (e.g. the PRE, CAREB and provincial harmonization initiatives) and broadly disseminated to the REB community.

G. Investigate the feasibility of more formalized requirements for sharing and/or posting of reviews.

The need for and importance of education is a top priority and a key issue for most of the REB community. Access to education can be considered as a way to improve quality of research ethics reviews, particularly if it is not just in relation to the rules and regulations, and content of the standards, but also and more helpfully, if it involves substantive ethical issues, and for example, sharing of reviews. The potential for developing a precedent database should be investigated. Transparent sharing of information and REB determinations in multi-site studies would help lead to more consistency in reviews, and could assist in the development of standards and metrics against which to assess REB performance.

Despite an apparent desire to innovate, REB administration mostly do not have the resources and are generally not trained researchers who have the requisite skills to conduct research into quality, effectiveness and efficiency of REB reviews. Even within the academic community, funding for this kind of investigation is generally sort term, fragmented and *ad hoc.* [6] Significantly, the results do not always involve or filter down to the REB administration community.

The working group believes that providing access to a suite of training and education materials (through PRE, CAREB, N2 and others) through completion of the registration process would provide an incentive to REBs to register their REBs and to continue to keep their registrations current. (See point 3, item C above).

H. Undertake a prioritization exercise to identify the top education/training priorities for REBs.

As part of our recommendations we advocate for a prioritization exercise to be undertaken to identify important educational and training needs. Such an exercise might draw on the reporting guideline community. Reporting guidelines are a checklist, flow diagram, or explicit text to guide authors in reporting a specific type of research, developed using explicit methodology [7]. The development process often include a Delphi survey – a multi-round consensus building process[8]. This process was used by Geisser and colleagues to develop a list of important aspects of ethics review[9], but has been used in research prioritization exercises [10]. Other approaches include the stakeholder engagement process developed by the UKs James Lind Alliance to brings patients, care givers and clinicians together in Priority Setting Partnerships (PSPs) to identify and prioritize the Top 10 uncertainties, or 'unanswered questions', about the effects of treatments that they agree are most important. The PSP could be used as a model to bring together researchers, the REB community, as well as funders to identify a 'Top 10' education and training requirements.

I. Re-visit the SHRER report recommendations and more broadly disseminate the SHRER document and the appendices.

The recommendations that the SHRER advisory committee made to the SPOR Working Group and the SPOR National Steering Committee in 2013 continue to resonate with the members of this working group. Despite the passage of three years, most of these recommendations continue to be worth pursuing. Given the passage of time, the results of this working group's activities, the development of CTO, and other developments within the research ethics field some changes have to be considered. However, the working group members (some of whom were on the SHRER advisory committee) were struck by the similarity in the recommendations made by both groups.

Related to this recommendation is the suggestion that appendices C.1 and C.2 to the SHRER report which reflect common elements for an REB initial application form for clinical trials, and the common elements for an adult informed consent form for clinical trials should be republished and more broadly disseminated, specifically targeting the various provincial streamlining and harmonization initiatives for information and possible consideration in the development of any common informed consent forms or application forms for their provincial initiatives.

J. Investigate the feasibility of a national on-line system for multi-center reviews

Quality, effectiveness, and in particular efficiency of REB reviews are enhanced by secure on-line systems that automate and streamline the ethics review processes and are accessible to REBs and researchers regardless of their physical location. On-line systems facilitate compliance, accessibility, transparency and reporting of metrics. They also facilitate collaborative sharing of information. The harmonized system in Quebec struggled to become accepted and effective until a shared on-line system was developed. OCREB has had an online system for five years, allowing it to vastly improve its

operations and productivity. CTO recognized from the outset that the only feasible way for it to develop an efficient system to support a single REB review of multi-centre research in Ontario was to create a single portal for the online submission and review of REB applications. British Columbia's harmonized review process which involves multi-party collaborated reviews, could not operate efficiently without an online system. Virtually all private REBs operating in Canada have online systems. They are an acknowledged cost of doing business without which, they would be unable to compete.

If Canada is serious about making research ethics reviews more efficient, it needs to investigate the feasibility of developing a shared on-line system or robust inter-operability of existing systems for at least those sponsored clinical trials that are being conducted at multiple sites across Canada.

5. CONCLUSION

At the outset, the working group suggested that a staged approach be taken. The data collected by the consultant reinforces the advisability of proceeding iteratively after consultation with and feedback from all stakeholders concerned with human research protections. We continue to feel that, as many respondents said, "it is important to take the time to do things properly and have the right people involved as further steps are taken."

6. REFERENCES

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7. GLOSSARY OF ACRONYMS

AAHRP - Accredited Human Research Protections

CAREB - Canadian Association of Research Ethics Boards

CCTCC - Canadian Clinical Trails Coordinating Centre

CGSB - Canadian General Standards Board

CIHR – Canadian Institutes of Health Research

CITI - Collaborative Institutional Training Initiative

CTO - Clinical Trials Ontario

HRA – Health Research Authority

IMC – Innovative Medicines Canada

IRB - Institutional Review Board

ICH-GCPs - International Conference on Harmonization: Good Clinical Practice: Consolidated Guidelines

ISED - Innovation, Science and Economic Development Canada

OHRP – Office of Human Research Protections

MIT - Ministry of Research and Innovation

MSSS - Ministère de la Santé et des Services sociaux (Ministry of Health and Social Services)

NIH - National Institute of Health

N2- Network of Networks

NPRM - Notice of Proposed Rulemaking

NSERC - Natural Sciences and Engineering Research Council of Canada

OCREB – Ontario Cancer Research Ethics Board

PRE - Panel on Research Ethics

PSPs - Priority Setting Partnerships

REB(s) - Research Ethics Board(s)

SACHRP - US Secretary's Advisory Committee on Human Research Protections

SHRER - Streamlining Research Ethics Review

SPOR – Strategy on Patient-Oriented Research

SSHRC – Social Sciences and Humanities Research Council of Canada

TCPS 2 (2014) - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans