CLINICAL TRIALS ONTARIO

External Review of the Newfoundland & Labrador Health Research Ethics Authority's (HREA) Health Research Ethics Board (HREB)

October 12, 2018

Submitted to:

Regina Coady

Chair, Board of Directors

Health Research Ethics Authority

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INTRODUCTION AND OBJECTIVES

This report is submitted in response to a request by the Newfoundland and Labrador (NL) Health Research Ethics Authority (HREA) for an external review of the Health Research Ethics Board (HREB).

The review was led and administratively supported by Clinical Trials Ontario (CTO) and was conducted from June to October 2018. The review included an on-site review, interviews, and review of HREB documentation and external comparative information following the visit. Detailed methodology is provided in Appendix 1.

The review focussed on four objectives as identified by the HREA:

> **Objective One***: Examine whether there are appreciable differences in the review timelines, process and decision outcomes related to the approval and continuing review of multi-center clinical trials in Newfoundland and Labrador compared to other jurisdictions:
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> **Objective Two**: Provide comparative metrics addressing REB workload (e.g. number of applications) and review timelines vs. REB resources of the HREA and HREB (both Committees).
>
> **Objective Three:** Conduct an environmental scan regarding accountability and reporting structures for REB operations personnel with comparable health ethics review volumes; Provide clarity on the roles of different REB operations personnel and the REB Chair.
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> **Objective Four**: Conduct an environmental scan regarding accountability models for REBs to governing institutions; Consider provincial, institutions, private, and disease specific governance models.

*As requested by the HREA for Objective One, the scope of review was limited to multi-centre clinical trials

OBJECTIVE ONE: Review Timelines, Process and Decision Outcomes

Review Timelines

A. HREB-CT Timelines

The Review Team was provided with the HREB Clinical Trials Committee (HREB-CT) metrics for the 2016 and 2017 calendar year, along with 13 study files representing the longest (five), average (three) and fastest (five) review times of approved multi-centre trials (as identified by the Research Ethics Office (REO).

The overall time to approval at HREB-CT has increased since 2016. The HREB-CT's metrics for 2016 indicate an average review time for Clinical Trial (Part A) applications is 75.5 business days (45 studies) compared to 105.4 business days (35 studies) in 2017. This represents a 39.6% increase in review time despite a 22.2% decrease in the number of approved studies. Of note, the average time applications spend with the HREB-CT/REO has increased by 77.8%, from 23.5 business days (2016) to 41.8 business days (2017), while the time spent with researchers has increased from 51.9 business days (2016) to 63.6 business days (2017), a 22.5% increase.

In September 2017 it appears response time to researchers began to increase. A review of the 13 study files provided revealed that prior to September 2017 most responses were sent back to the research team within one week (7 calendar days) or less and the letter outlining the requested HREB-CT revisions (i.e., following the full board meeting) was typically sent about 5 calendar days after the meeting. Starting in September 2017 response times of 15-30 days are observed. Due to the limited data/studies provided it is difficult for the Review Team to determine if this is a trend that continues to present day.

B. HREB-CT Timelines Compared to Other REBs

HREB-CT timelines were compared to the timelines of other REBs in two ways. First they were compared to review times for multi-site clinical trials reviewed through the Clinical Trials Ontario (CTO) system. Second, the review times for a selection of trials approved by the HREB-CT were compared to REBs in Ontario or elsewhere in Canada that reviewed the same trials.

Comparison to CTO REB Review Timelines

In the province of Ontario 17 REBs are *CTO Qualified* to act as a Board of Record for any study submitted through the CTO system (the Board of Record is the single REB that reviews the study on behalf of

multiple participating sites). REBs range in size, focus and workload and are publicly listed on the CTO website (www.ctontario.ca).

The average time to approval for the initial application for multi-centre clinical trials reviewed by Ontario REBs working in CTO Stream is approximately 62 business days (87.5 calendar days).

The average review time for multi-site clinical trials reviewed through CTO Stream is 68.5% faster than the 104.5 business days for studies reviewed by the HREB-CT. It should be noted that the HREB-CT review times include both multi-site studies and studies that are conducted only within Newfoundland and Labrador.

Comparison of Review Times for Selected Clinical Trials

The Review Team compared the 2017 approved study list (provided in the 2017 calendar year metrics) to clinicaltrials.gov data to determine which of the clinical trials were multi-centre and involve other REBs in Canada. Seven studies were identified as potential 'comparator' studies. Where possible, the Review Team used the data in clinicaltrials.gov to predict the likely REB of Record for the clinical trial site and requested information from the REB of Record. REBs agreeing to participate in the process were asked to provide review timeline information and a general description of ethical issues (if applicable) for those comparator studies they reviewed.

Comparison Study One

This study was identified by the REO as one of the HREB-CT's longest reviews for a multi-site clinical trial (of those approved in 2017). The HREB-CT had the longest review period (time from initial submission to approval) at 322 calendar days, compared to the other REBs who reviewed and approved the same study in 62 calendar days, 93 calendar days and 206 calendar days. The HREB-CT time represents a 419% increase compared to the shortest review period (REB 1), and 56% increase compared to the second longest review period (REB 2). The review period for REB 1 and REB 2 included the December holiday. REB 2 indicated that the length of the review period for this study was atypical, and that approval is typically issued in 2-3 months.

Also of note, REB 1 deemed the study to be minimal risk and conducted a delegated review, and REB 2 and REB 3 reviewed the study at one REB meeting. HREB-CT reviewed this study at two REB meetings; for the second review, the study was not reviewed at the originally scheduled meeting due to time constraints and delayed for two weeks for review at a subsequent REB meeting.

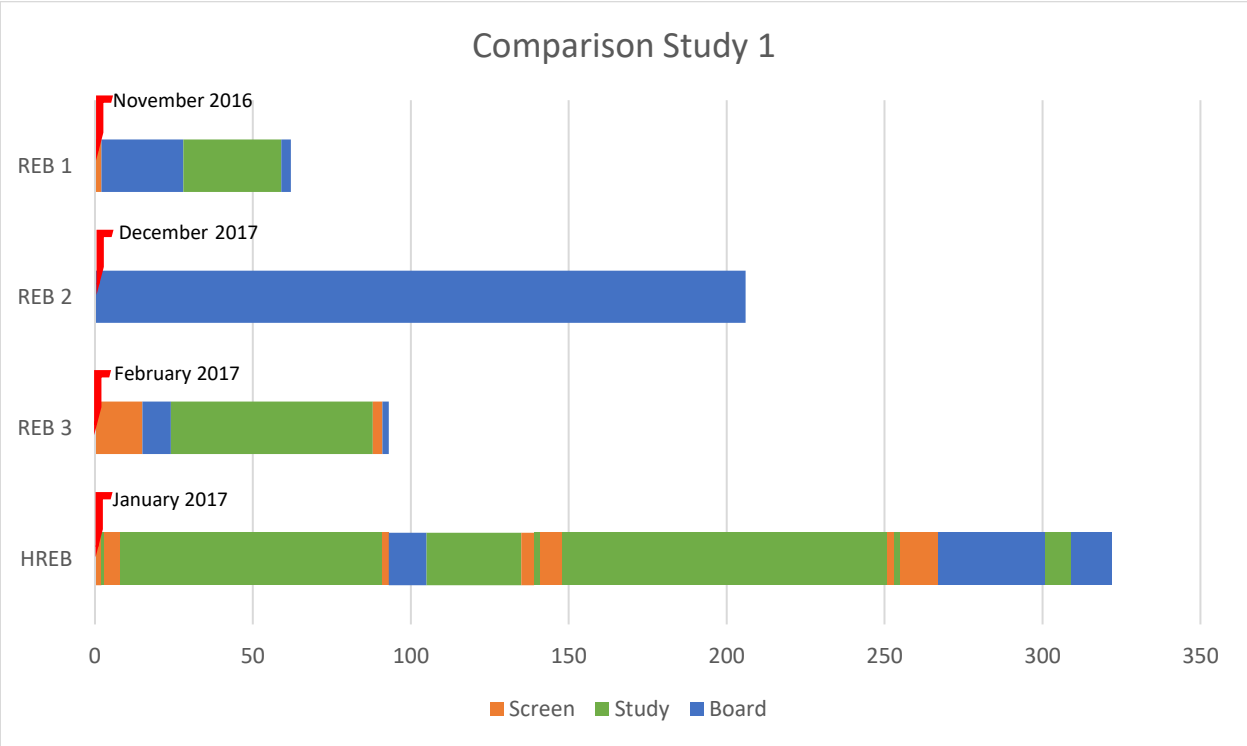
With respect to the HREB-CT review period, the Review Team notes the application spent a substantial amount of time with the study team. At the HREB-CT, the application spent 93 calendar days (28.9% of the review period) with the HREB-CT/REO, and 229 calendar days (71.1% of the review period) with the study team. In comparison, the application spent 50% of the review period with the REB 1 (50% with the study team), 100% of the review period with REB 2, and 31.2% of the review period with REB 3 (68.9% with the study team). While the application spent a similar percentage of time with the HREB-

CT/REO and REB 3 (28.9% and 31.2% respectively), REB 3 had the shortest review period; the HREB-CT review period represents a 246.2% increase in comparison.

This study is reviewed later in this report as a Case Study on decision outcomes.

Legend

Screen: Represents time spent after submission and prior to the application being accepted for review (full board or delegated), when known.
Study: time spent with the research team (i.e., after the application has been sent back and before the application has been re-submitted)
Board: Represents time spent with the REO/REB that is not screening. For REBs without screening activities, this will comprise the full allotment of time with the REB.



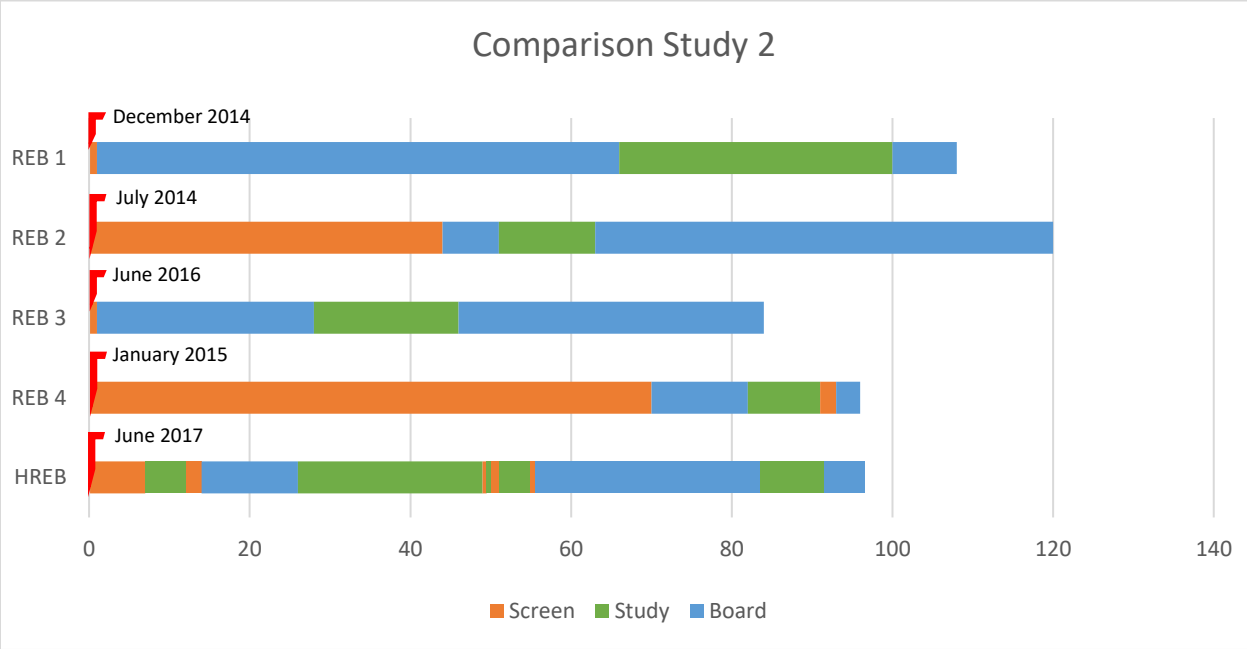
Comparison Study Two

This study was identified by the REO as one of the HREB-CT's shortest review times for a multi-site clinical trial (of those approved in 2017). Of the five REBs who approved this study and contributed data, the HREB-CT had the second shortest review period (time from initial submission to approval). The shortest review period was 84 calendar days (REB 3), the HREB-CT review period was 95 calendar days, and longest was 120 calendar days (REB 2).

At the HREB-CT, the application spent 56 calendar days (58% of the review period) with the HREB-CT/REO, and 40.5 calendar days (42% of the review period) with the study team. In comparison, the application spent 68.5% of the review period with the REB 1 (31.5% with the study team), 90% of the review period with REB 2 (10% with the study team), 78.6% of the review period with REB 3 (21.4% with the study team), and 90.6% of the review period with REB 4 (9.4% with the study team).

The Review Team also notes that the study was submitted to three REBs in late 2014/early 2015, the fourth REB in mid-2016, and was not submitted to the HREB-CT until mid-2017.

The HREB-CT reviewed this study at two REB meetings, while all other REBs reviewed the study at one.



Comparison Study Three

There was only one comparator REB identified for this study and the HREB-CT had the shortest review period (time from initial submission to approval) at 78 calendar days, compared to 90 calendar days at REB 1. The application spent less time with the HREB-CT/REO (37.6% of the review period) and more

time with the study team (62.4%); the opposite was true at REB 1, where the application spent 61.1% of the review period with the REB (38.9% with the study team).

Both REBs reviewed the study at a single full board meeting.

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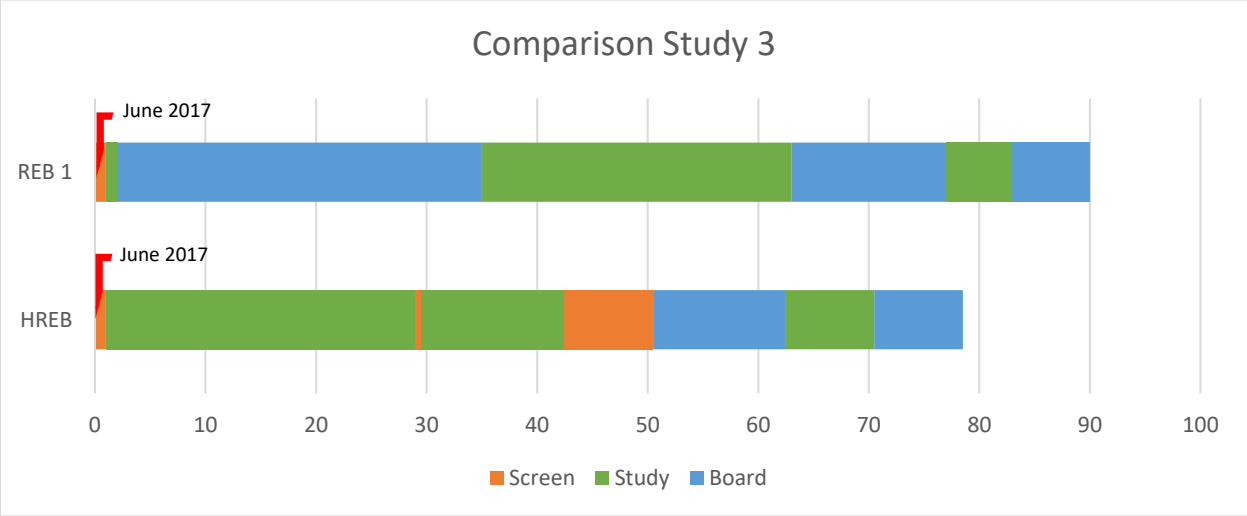


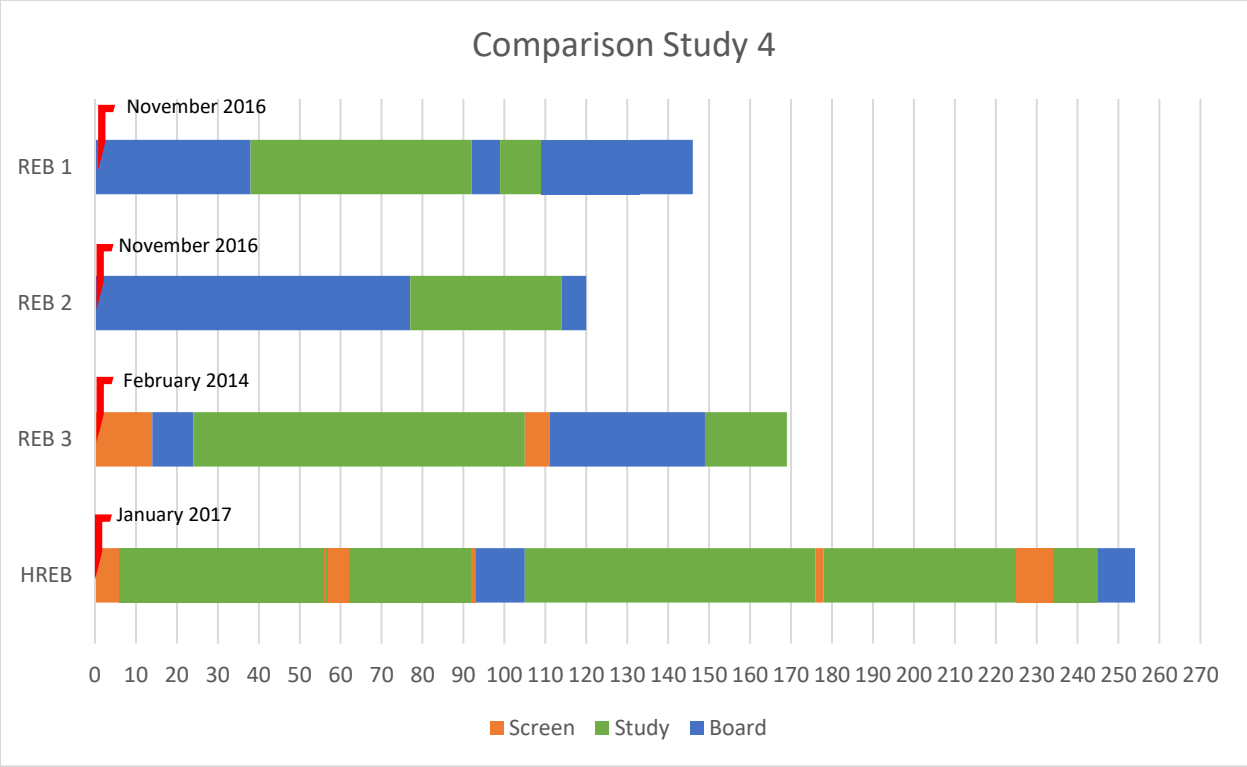
Comparison Study Four

This study was identified by the REO as one of the HREB-CT's longest review times for a multi-site clinical trial (of those approved in 2017). Of the four REBs who approved the study and contributed data, the HREB-CT had the longest review period (time from initial submission to REB approval) at 253 calendar days.

In comparison, the review period was 146 calendar days at REB 1, 120 calendar days at REB 2 and 169 calendar days at REB 3. This represents a 111.7% increase compared to the shortest review period (REB 2), a 50.5% increase compared to REB 3, and a 43.9% increase compared to REB 1.

At the HREB-CT, the application spent 44 calendar days with the REO/HREB-CT (17.4% of the review period), and 209 calendar days with the study team (82.6% of the review period). In comparison, the application spent 56.2% of the review period with REB 1 (43.8% with the study team), 69.2% of the review period with REB 2 (30.8% with the study team), and 40.2% of the review period with REB 3 (59.8% with the study team).

Of note regarding REB 3, the study team submitted an amended protocol with their first re-submission (i.e., in response to the REB's original questions and requests for changes), necessitating a longer review period due to an additional full board review (this would not have been required had the amendment not been submitted).

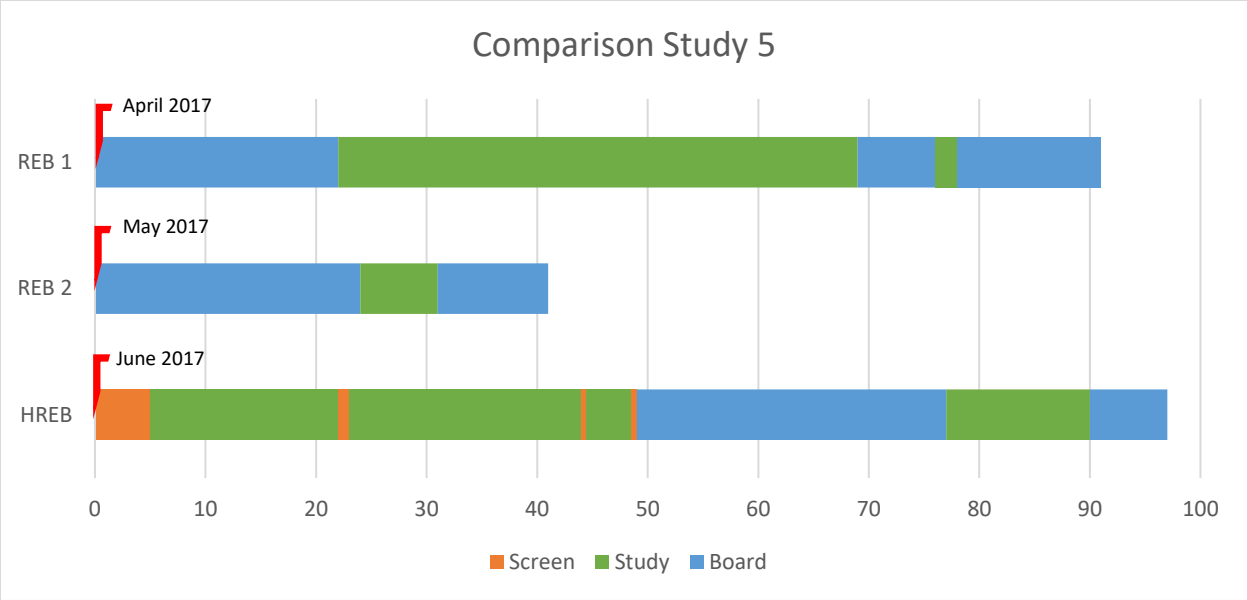


Comparison Study Five

This study was identified by the REO as one of the HREB-CT's shortest review times for a multi-site clinical trial (of those approved in 2017). While the HREB-CT had the longest review period of the three reviewing REBs at 96 calendar day, it is comparable to that of another reviewing REB (REB 1, 91 calendar days).

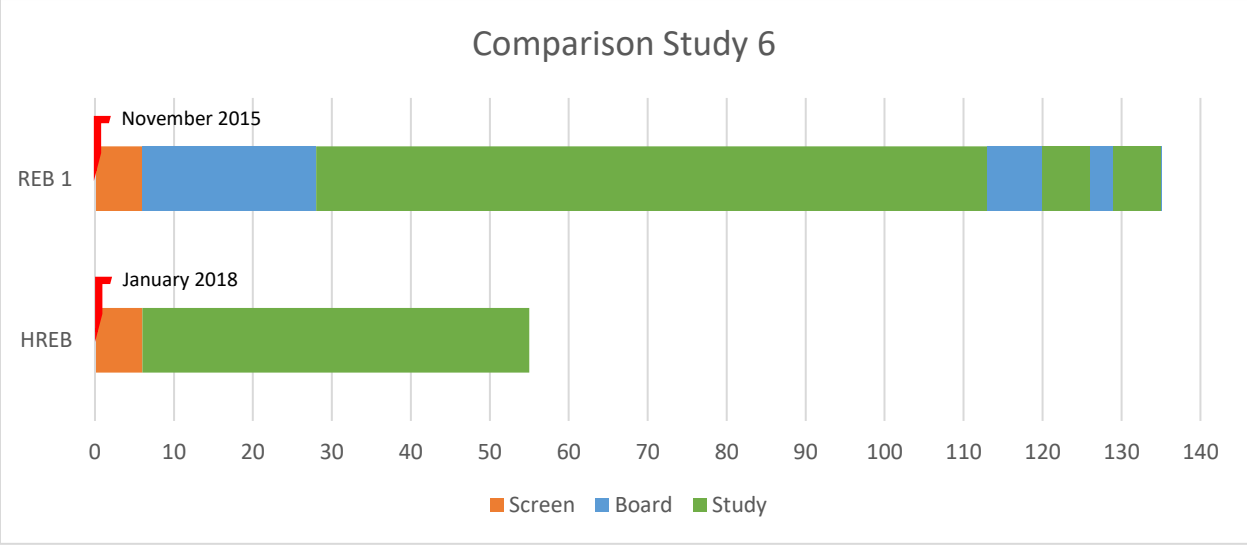
For the HREB-CT review period, the application spent 41 days with the REB/REO (42.7% of the review period) and 55 days with the study team (57.3% of the review period). For REB 1 (whose review period was comparable to that of the HREB-CT), the application spent 42 days with the REB/REO (46.2% of the review period), and 49 days with the research team (53.8% of the review period).

REB 2 had a substantially shorter review period compared to both REB 1 and the HREB-CT, at 41 calendar days.



Comparison Study Six

This study was withdrawn by the research team in Newfoundland and Labrador prior to approval by the HREB-CT as the study was recruiting faster than expected and the Sponsor anticipated that accrual would be complete prior to approval by the HREB-CT. This study was submitted to REB 1 in November 2015, but was not submitted to HREB-CT until January 2018.

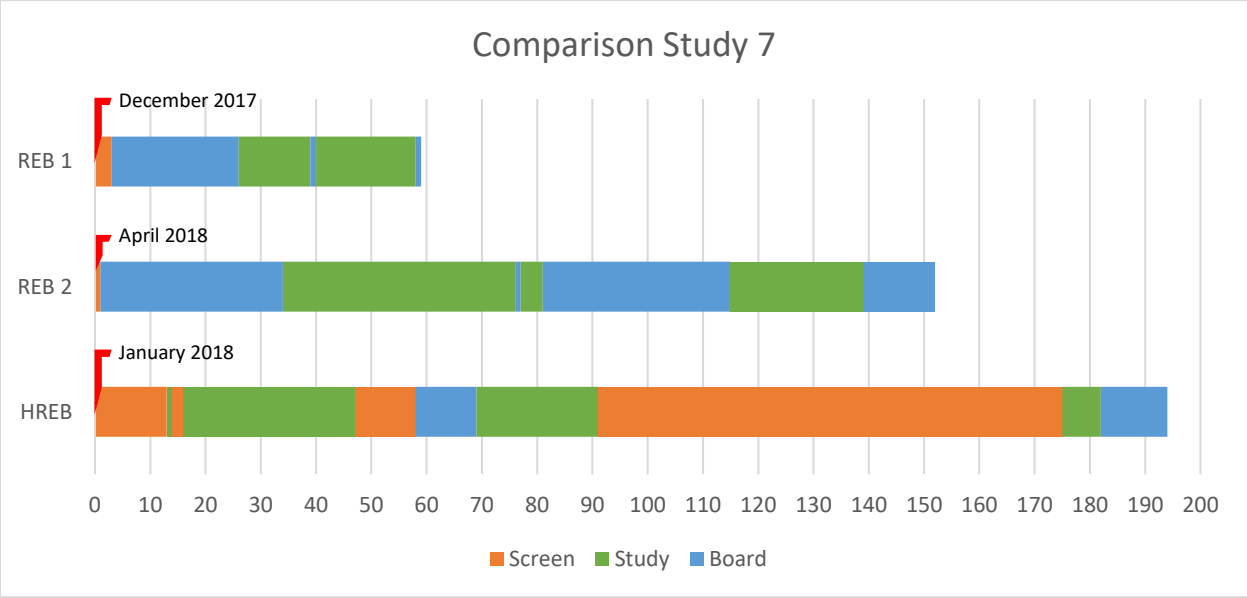


Comparison Study Seven

The HREB-CT review period for this study was 194 calendar days, the longest of the three REBs (REB 1, 59 calendar days; REB 2, 152 calendar days). This represents a 228.9% increase compared to the REB with the shortest review period, and a 27.6% increase compared to the other reviewing REB.

The Review Team notes that this application spent more time with the HREB-CT/REO compared to the other reviewing REBs. At HREB-CT, 133 days (68.6% of the review period) was spent with the HREB-CT/REO, compared to 82 calendar days (47.5%) with REB 1 and 28 calendar days (53.9%) with REB 2.

Additionally, REB 2 noted delays in their review due to staff holidays and technical difficulties (occurring approximately between days 85-115).



Discussion:

Of the seven comparator studies reviewed:

- One study was withdrawn from the HREB-CT review process by the sponsor/study team as it was unlikely the review would be completed before recruitment closed (Comparison Study 6)
- The HREB-CT had the longest review period for 4 of the 6 approved studies
- The HREB-CT did not have the longest review period for 2 of the 6 studies
    - In one study, the HREB-CT had the shortest review period (Comparison Study 3 with 1 comparator REB)
    - In the other, the HREB-CT had the second shortest review period (Comparison Study 2 with 4 comparator REBs)
- In 4 of the 6 approved studies, the application spent more time with the study team than with the HREB-CT/REO; however, the majority of times the application was returned to the researchers it was due to screening vs. feedback from the HREB-CT

There were several HREB-CT/REO processes that seemed to impede review times.

The **screening process** appears to substantially delay the review of new studies by the REB. Based on the information provided for the 13 pre-selected clinical trials, which represent the fastest, average and longest review periods (i.e., time from submission to approval) for multi-site clinical trials submitted in 2017, the average time from initial submission of the study to first review by the HREB-CT was 75.7 calendar days (median 71, range 14-169). Studies required an average of 3.2 re-submissions prior to being accepted for full board review (median 3, range 1-6). With respect to the 6 approved comparator studies, in all but two instances (both on Comparison Study Two), the HREB-CT received the application later in the review period than all other reviewing REBs.

There were more **re-submissions** (and associated screening events) in Newfoundland and Labrador for every study compared to every REB who contributed data. A review of the 13 pre-selected studies highlighted repeated instances where the initial queries to investigators were not sufficiently detailed to support research teams in providing all required information with the first re-submission of the application. For example, a common phrase is "please clarify response to question X". The Review Team found that it is often unclear what information would be required to satisfy the screening criteria, and the repeated instances of re-screening suggest that it is not clear to research teams as well. In many cases, once the research team provided additional information, further clarifications were required. The Review Team also noted instances where researchers seeking additional clarification or guidance were not provided assistance. For example, a research team seeking clarification regarding the REB's request to remove redundant information was informed that it was the team's responsibility to determine which information was redundant.

Subsequent review of the minutes and agendas for the 2018 meetings suggest that an unusually high **number of applications are not reviewed at the originally scheduled full board meeting**. Review of the meeting minutes from 2018 identified 9 'new business' applications (representing 6 new studies) and 8 'other business' applications (amendments) that were not reviewed at their originally scheduled REB meeting. Of particular note, three studies were delayed for two meetings (April 19 and April 23, 2018) before being reviewed by the HREB-CT at the third meeting (May 3, 2018). The Review Team also noted instances where an application could not be reviewed at the full board meeting because either (a) a reviewer indicated they required access to the IB/PM to verify the consent changes, (b) the primary reviewer was absent, or (c) quorum was lost after the start of the meeting.

Review Process

To develop an understanding of the review processes of the HREB-CT information was derived from several sources including HREB-CT policies and procedures, the review of HREB-CT study files, meeting minutes and agendas, and interviews with the REO team, REB members and researchers.

Interviews with researchers revealed frustration with the review process and a perceived emphasis on administrative issues vs. ethical issues. Researchers expressed concerns that delays in research ethics review are putting patients in Newfoundland and Labrador at a disadvantage with respect to access to clinical trials available elsewhere in Canada. One researcher highlighted an instance where a participant travelled outside of the province to access a study, and how most patients do not have the resources to do this.

Interviews with researchers and results from a recent survey indicated there is sentiment within the research community that the HREB-CT and REO take an adversarial approach to research teams. There is a perceived lack of collaboration and constructive feedback on how to make research better for participants.

Researchers interviewed conveyed that colleagues have 'given up' on research and reflected on their own declining clinical trial opportunities. Researchers indicated that industry sponsors are not selecting sites in Newfoundland and Labrador due to long review timelines and the administrative burden involved in getting studies approved by the HREB-CT. Of particular concern, the Children's Oncology (COG) program appears to be at risk. The importance of clinical trials in pediatric oncology cannot be understated; the consequences of losing COG status would be profound and long standing to children with cancer in Newfoundland and Labrador.

The Review Team provides the following observations regarding HREB-CT review processes:

1. The HREB-CT and REO appears to spend significant time and effort on administrative considerations

The mandate of the REB, as defined by TCPS 2, is to review the ethical acceptability of research. Most interviewees acknowledged that significant time and effort is spent on administrative considerations that often do not lead to substantive changes to the studies overall. Administrative issues referred back to research teams for correction included typographical or transcription errors in the REB application form, the inclusion of information cut-and-pasted from the protocol (e.g., eligibility criteria), and REB application information not matching other documents (except where lay language has been specifically requested).

REB members and REO personnel indicated decreasing quality in the submissions received. Review of the study files and meeting minutes suggests the HREB-CT and REO are attributing quality issues to the content of the application form, and not to the study itself. Interviews with HREB-CT members and researchers highlighted that at the end of the review process there were little to no substantive changes to the study. There was no external documentation or evidence provided which suggests that the quality of research or qualification of the researchers in Newfoundland and Labrador was suboptimal.

Based on a review of meeting minutes the HREB-CT appears to have become more focused on administrative aspects over time. Meeting minutes from 2017 indicate discussions at the time did not seem to focus on administrative aspects of the application/consent, nor were there as many requests for administrative revisions as what is seen in 2018.

The focus on administrative considerations is also evident during the review of post-approval activities (i.e., amendments). The Review Team noted instances of amendment reviews at the full board where for example, the HREB-CT determined that approval for the revised protocol would be held until a typographical error in the REB application form or the informed consent form were corrected.

2. Screening does not appear to provide measurable improvement to the quality of the review process and screening requests can lack understanding of study-specific context

There are no written guidelines describing the REO screening process or requirements. Interviews with the REO highlighted that screening ensures the application is of sufficient quality to be reviewed by the HREB-CT, enabling the HREB-CT to focus on substantive ethical issues. Interviews with REO personnel highlighted that some questions on the application form are not relevant to the HREB-CT review but because they are present acceptable responses are required as a condition of approval (e.g. parties to study agreements).

The Review Team was informed that the REO had attempted to decrease the amount of screening but felt these efforts were unsuccessful as this approach resulted in more applications being sent back for an additional full board review (after the first review). However, despite repeated instances of re-screening, the HREB-CT meeting minutes highlight that the HREB-CT is continuing to 'catch' administrative considerations during their review.

Review of the pre-selected studies also highlighted instances where the screening process resulted in queries to researchers that the Review Team felt lacked understanding of study context. For example, for one of the pre-selected studies reviewed, the initial screening revisions requested changes to the informed consent form to insert HREB-CT template wording regarding pregnancy and 'end of study' requirements including access to the investigational drug or device. However, the template wording clearly did not apply to this study (an exercise intervention), and these requests were rebutted by the research team. A subsequent screening letter from the REO indicated that the research team must provide further information/justification as to why the template language didn't apply.

In another instance, the screener requested that the research team remove information indicating that participants would not be reimbursed should the study results be used to generate intellectual property (IP) or otherwise commercialized by the sponsor, with the indication that this statement is only applicable to the optional research component. This content was not removed by the study team and the language was ultimately approved by the HREB-CT.

Interviews with researchers highlighted that it is challenging to respond to screening questions that clearly did not apply or suggested an incorrect understanding of the study by the screener. They expressed frustration in the added workload and perceived delay these questions cause.

3. The review process does not appear to be proportional based on level of risk to participants

There appears to be no delegated review process for studies that constitute no more than minimal risk; it seems like all studies are being subject to the full board review despite the clear difference in the level of risk to participants. Several of the full board reviews listed in the agenda were of studies not considered to be clinical trials. These studies may involve minimal risk and could potentially be delegated rather than being reviewed at full board meetings. This issue also applies to amendments; an amendment noted in the HREB-CT minutes underwent delegated review at the Ontario Cancer Research Ethics Board (OCREB) but, at the HREB-CT, it was assigned to a full board meeting and then deferred to the next meeting as the primary reviewer was not present.

4. HREB-CT meetings are long and frequent relative to the number of applications reviewed.

The HREB-CT meets twice a month and despite a limited number of applications to be reviewed often defer applications due to time constraints. When applications are not reviewed due to time constraints it is not clear to the Review Team how the HREB-CT determines which application(s) will be deferred.

There appears to be an unusual amount of time dedicated to the review of the study-specific informed consent form (ICF) during REB meetings; interviews with REO/HREB-CT suggested that it was not uncommon for ICF review to take one hour per study at the meeting. In the experience of the Review Team, this is not a common practice amongst REBs and may explain why the HREB-CT is facing challenges with reviewing all studies within the allotted meeting timeframe.

In the experience of the Review Team it is not uncommon for a REB to review 10-12 new applications for interventional studies in a single three hour REB meeting. The 2018 HREB-CT meeting minutes reviewed indicated a range of 1-7 new applications scheduled per meeting, with additional 'other business' items (e.g., amendments, responses). The highest amount of new studies reviewed in a single meeting was five.

5. The HREB-CT appears to be responsible for data custodian requirements normally outside the purview of the REB.

Based on a review of the meeting minutes it appears the HREB-CT has been delegated or otherwise become responsible for reviewing the letter sent to the data custodian requesting access and confirming that this letter has been submitted to the custodian, before HREB-CT approval can be issued. The OIPC guidance[i] "Disclosure of Personal Health Information for Research Purposes: Guidance for Researchers and Custodians of Personal Health Information" specifies that researchers must explicitly identify in detail in the REB application the information they intend to access (or collect) from the custodian and/or the specific information they intent to collect directly from participants as part of the project. The OIPC further specifies that the custodians have accountabilities and that researchers should expect to have their REB approval documents reviewed by the custodian. The guidance does not appear to require that the REB review and approve the request letter to the custodian or provide the REB with the authority to determine whether the letter submitted is sufficient for the purposes of the data custodian, but the minutes suggest the HREB-CT is responsible for this.

6. The REO/HREB-CT have not adopted current best practice, do not have updated SOPs, and the tools and templates could be improved to better support the review process.

The HREB-CT has not adopted the Canadian Association of Research Ethics Boards (CAREB) Guidance on Reporting of Unanticipated Problems Including Adverse Events to Research Ethics Boards in Canada[ii]. This guidance has been adopted by many REBs across Canada and is intended to reduce unnecessary reporting to the REB and improve the REB's ability to evaluate those unanticipated problems that may potentially impact the rights, welfare or safety of research participants.

Standard Operating Procedures (SOPs) have not been updated since March 27, 2012 and appear to be missing content that would normally be expected in REB SOPs.

The Consent Form Template contains requirements unique to the HREB-CT which may not offer benefits to participants and do not appear to accommodate study-specific requirements. For example, the template indicates that participants must be informed of the number of individuals that have been exposed to drug/device to date. Such information will always be out of date (meaning that incorrect information is presented to participants) and requires that the ICF be updated with each new IB/PM released. In many cases the template indicates that research teams must select from existing options, instead of inserting the details relevant for the specific study. This may lead to incorrect information being provided to participants and an administrative burden to researchers who are required to justify why they aren't selecting from these options in the consent form Checklist (even when it is evident that the template wording is incorrect/out of context for the study).

The initial application form could better support the HREB-CT in assessing the ethical acceptability of studies or local implementation of the study. Questions regarding local implementation are not sufficiently clear or detailed, resulting in frequent and common screening questions. For example, project start date is requested but it is not specified if it is the start date for the study overall, or the local start date. Interviews with the REO indicated that there is interest in revising the application forms, but technical difficulties in implementing changes.

Decision Outcomes

Researchers conveyed examples of studies submitted for ethics review that were either not approved at all or not approved before the study was closed to recruitment, and were approved elsewhere in Canada and/or internationally. An example was shared with the Review Team (this study was not identified as in scope for the review) where the approval was significantly delayed and issued only after the researcher was able to obtain guidance that supported approval from the Secretariat for the Responsible Conduct of Research.

The Review Team notes the high proportion of studies requiring a full board review of the researcher's response to REB queries, as suggested by the minutes and agenda for the 2018 meetings. Based on minutes the HREB-CT required full board review of the responses for 11 'new business' applications, representing approximately 27% of the sample. In the experience of the Review Team this is uncommonly high. In many instances it was not clear to the Review Team why full board review of the re-submission was required. This is particularly noted in instances where the meeting minutes noted "The Board found no major ethical concerns with this study" but determined full board review of the response was required.

It can be challenging to compare REB decision outcomes generally; however, the case study below provides a detailed example of the HREB-CT compared to three other REBs reviewing the same study.

Case Study: Comparison Study One

This study includes an optional research component in which participants could choose whether or not they agreed to allow their bio-specimens to be banked (stored) for future undefined research. Consent for unspecified future research is sometimes called 'broad consent'. This study was submitted to the HREB-CT in January 2017.

HREB-CT Review:

The researcher was informed that "Broad consent for future research is not acceptable to the HREB", and that the future use of the tissue must be limited. As part of the researcher's response, the HREB-CT was informed that the policies of the academic cooperative group leading the study (located in the US) does not support additional restrictions on future use, and referenced the upcoming changes to the US Common Rule as supporting evidence that this policy was unlikely to change. The HREB-CT response was the same; broad consent is unacceptable.

The research team sought further clarification from the REB, and provided additional information from the Canadian sponsor. Of note, the Canadian sponsor indicated that they had not received objections from other Canadian REBs, to which it appears that the REO responded indicating they had spoken with other REBs that approved the protocol who indicated that they were unaware of the issue. The researcher was informed the HREB historically did not approve broad consent for unspecified research as it would not meet the consent requirements outlined in ethics regulations. It appears as though the REO referenced a guidance document from another REB as support for their position, despite a key difference in context: the REO appears to have referenced mandatory banking for future unspecified research (i.e., participants cannot join the main clinical trial unless they agree to allow their samples to be banked for this purpose), while the study in question involved optional banking for future unspecified research (i.e., participants could join the main study regardless of whether they accepted or declined the banking of their samples).

No further discussion is noted in the file provided, but approximately three months later, the informed consent form was re-submitted with additional wording explaining that participants will not be asked to provide additional consent if their samples are used and that their study doctor will not necessarily be involved in the research that will occur on the samples. The HREB-CT reviewed the revised consent and requested additional changes relating to risks and access to health records; the application was then re-submitted and approved by the HREB-CT.

Review by other REBs:

REB 1 deemed this minimal risk research (i.e., research in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that relate to the research). No major ethical issues were identified.

REB 2 raised questions regarding collection and use of data from participants who were consented but subsequently deemed ineligible. Following discussions between the REB, research team and sponsor, the REB concluded that the consent form should be updated to state clearly that those who are deemed ineligible may continue on the study protocol and that data collection would continue for these participants.

REB 3 did not note any ethical concerns, but requested a privacy impact assessment and clarification on tissue collection and use of identifiers.

Observations:

The HREB identified broad consent as unacceptable on the basis that it would not meet the consent requirements outlined in ethics regulations. The Review Team is unaware of any regulations or ethical guidelines that prohibit broad consent, but notes that many REBs do not feel broad consent/future unspecified research is acceptable as a *mandatory* component of research [an example of such a policy can be found at the University of British Columbia (UBC)].

The REO also indicated that consultations with other REBs indicated that they "were unaware of this issue". The Review Team is unclear as to whether this means that other REBs did not perceive broad consent to be an issue in the context of this study, or whether the other REBs were not aware that the study involved broad consent. A number of REBs in Canada, including the Ontario Cancer Research Ethics Board (OCREB) and the University of British Columbia have had policies[iii] or consent templates[iv] addressing broad consent for optional future research for some time; these policies and documents focus on ensuring participants are made aware of key information through the consent process that may affect their willingness to participate, including the lack of specificity regarding what the samples may be used for in future.

Lastly, the Review Team notes that there were a number of instances where the research team/sponsor requested clarification from the REO and HREB-CT. Little guidance or support was provided; the research team was informed multiple times that broad consent was unacceptable and that future research would have to be limited, even after the HREB-CT was informed that was not possible in the context of this study.

Differences in opinion will arise, and meaningful opportunity for discussion between the researcher and REB can help to avoid the escalation of issues and formal requests for reconsideration or appeal. Several researchers referenced a dramatic shift in communication between the HREB and researchers in the past 1-2 years. Both the REO and researchers described a deteriorating line of communication between the office, the Co-Chair and the researchers during this time. At the time of the review there appeared to be no direct means of communication between the Co-Chair and researchers.

As noted in the TCPS "Evaluating the ethics of research involving humans is not, and cannot be, an exact science. The interpretation and application of the articles and principles to particular circumstances will always be part of the exercise". It is not reasonable to expect that every REB will review the same study in the same way with the same outcome. The example presented here demonstrates that REBs will focus on different issues in their review.

In this example the HREB-CT took a significantly longer time to approve the study than the other REBs. It appears that policy considerations and communication challenges between the REO, HREB-CT and researcher were contributing factors to the delay. Article 11.4 of the TCPS states that both researchers and REBs are responsible for ensuring risks are justified by potential benefits and appropriately minimized. Although the respective roles of each need to be respected and the REB remain independent in its ethical decision making, an environment in which researchers and REBs can

communicate effectively and collaborate to achieve these common responsibilities is important. This helps to support a high-quality and efficient ethics review process and informed and thoughtful ethical considerations for participants on studies.

Incidental Observations

The Review Team notes that producing the requested study records required considerable time and effort for the REO. One component of this delay appears to be attributable to the electronic REB (eREB) system not maintaining a complete record of all study transactions (responses to emails sent from the eREB system are not saved within the eREB system and have to be retrieved otherwise). When an amendment is submitted and changes are requested the changes are made to the original document so it is not possible to compare what was submitted to what was approved.

The Review Team was also advised that researcher's names needed to be redacted from all study files due to legislation in Newfoundland and Labrador. This is unusual in the context of an external review (all reviewers signed confidentiality agreements) and caused delays in the receipt of study files; only five were available for review while the Team was on-site.

Lastly, there appeared to be difficulty in obtaining certain metrics/key information from the eREB system.

These challenges added complexity to the review and reduced the ability of the Review Team to assess all factors.

OBJECTIVE TWO: REB Workload and Resources

HREB Workload

The tables below provide the number of applications and the average review timelines for the HREB-CT, the HREB Non-Clinical Trial Committee (HREB-NCT) and the number of approved applications in 2017 for both committees.

Overview of HREB-CT review timelines (2017)

HREB Clinical Trial Committee				
	Number of applications	Average days with researcher	Average days with HREB	Total average days
HREB Application for Ethics Review of a Clinical Trial (Part A)	35	63.6	41.8	105.4
HREB Application for Ethics Review of a Clinical Trial (Part B)	3	3.7	8.0	11.7
HREB Application for General Research	6	69.1	37.7	106.9
HREB Secondary Use/Chart Audit Application	5	18.7	57.2	75.9

Overview of HREB-NCT review timelines (2017)

HREB Non-Clinical Trial Committee				
	Number of applications	Average days with researcher	Average days with HREB	Total average days
HREB Application for General Research	142	30.5	15.8	46.4
HREB Secondary Use/Chart Audit Application	75	37.8	17.3	55.8

HREB: Current REO Resources

The REO personnel interviewed are passionate and dedicated. These individuals are working extra hours to keep up with the current workload. There is interest in improving REO processes, but a lack of clarity on how to proceed.

At present there is one Receptionist and two Secretaries (one for each Committee), with one Ethics Officer supporting both Committees. In the experience of the Review Team, REOs using electronic REB

systems typically require less administrative support and increasing volume is typically supported by the addition of Coordinator (Ethics Officer)-level positions.

The current structure leaves little opportunity for the REO to perform higher-level screening tasks or for the REO to undertake other work typically associated with a REO such as SOP updates, education, preparation of guidance documents, process improvements, etc.

REO Workload/Staffing Comparison

The table below provides the number of reviews (by type) and REO personnel for the HREB and four comparator REBs.

REO Resources Comparison

	Initial Reviews	Continuing Reviews/ Renewals	Amendments	Reportable Events	Personnel	Electronic System?	Meetings Per Month
HREB Clinical Trial Committee	66	192	276	565	Receptionist (1) Secretary (2) Ethics Officer (1) Director (1)	Yes	2
HREB Non-Clinical Trial Committee	217	103	93	103			2
REB A	80	210	420	71	Manager (1) Coordinator (1)	No	1
REB B	230	580	400	92	Manager (1) Coordinator (1)	Yes	1
REB C	350	700	900	150	Manager (1) Coordinator (2) Administrative Assistant (1)	No	1
REB D	600	1550	1140	325	Manager (1) Coordinator (1) Administrative Assistant (1)	Yes	1

It is understood by the Review Team that the Ethics Director position also supports the HREA. If the Ethics Director allocates 50% time to the REO, the REO has 4.5 FTE's, with 3 of the positions being administrative. This staff complement is higher than all of the other REBs and it is particularly noteworthy how many administrative positions there are compared to the other REBs which have at most 1 administrative position. It is noted that the HREB is the only of the REBs to have two meetings (per Committee) per month.

On the basis of volume the REO should be sufficiently resourced with respect to the number of FTEs to support the activities of the HREB and has greater resource than the comparator REBs. The nature of

the review processes conducted by the REO (e.g. intensive screening activities by multiple individuals, frequent back-and-forth between the REO, HREB and research teams, deferrals of reviews to subsequent meetings, four meetings per month) all impact the timelines and resource requirements of the current REO. The HREA has significant opportunity to improve review timelines and REO office efficiency by making changes in the review process. Specific recommendations include:

Streamline administrative tasks:

- Revise the screening procedures:
    - Eliminate step-wise screening by multiple individuals;
    - Ensure requests to investigators are clear and sufficiently detailed and consider the specific nature of the study being reviewed;
    - Reduce or eliminate administrative tasks that do not appear to improve the ethics review process or quality of submissions [e.g., eliminate the Consent Form Checklist, remove or revise certain questions in the REB application form(s)];
    - Ensure individuals screening applications or otherwise involved in the review process are appropriately qualified
    - Develop criteria for changes to the ethics submission that require resolution prior to going to the REB for review (i.e., missing documents) vs requested (and necessary) changes that can be sent back in conjunction with HREB feedback
    - Provide clear instructions on REB submission requirements, deadlines and screening procedures.
- Adopt the Canadian Association of Research Ethics Boards (CAREB) Guidance on Reporting of Unanticipated Problems Including Adverse Events to Research Ethics Boards in Canada.
    - The Review Team notes that the volume of reportable events relative to the number of ongoing studies is quite high and suspects that many of these events do not require REB reporting under the CAREB criteria. This will reduce administrative workload while ensuring appropriate oversight.
- Identify opportunities to improve or maximize functionality of the electronic REB system.
    - Examples include revisions to application forms and improved reporting capabilities.
- Improve templates and application forms to reduce the need for back-and-forth.

Improve Outreach and Communication

- Improve outreach and connection with the research community;
- Create connections with the organizations/institutions submitting to the HREB to better understand the needs of the diverse research community, and to understand the research administration process in these different organizations;
- identify available resources such as local experts or ad hoc reviewers with specific expertise to support the HREB reviews
- develop educational resources to help research teams submit better research applications
- Review REO/HREB email and letter templates to support improved communication (the language in some communications does not seem to support collaboration).
- Create relationships with other REOs at other REBs to increase exposure to alternate review processes and REO interactions with the REB and Research teams

The Review Team also notes the impact of the full board meeting schedule on REO resources. Considering the workload involved in agenda and minute preparation, meeting organization, time spent in the meeting, and other administrative aspects, the frequency of meetings is likely to have a substantial impact on the REO. In the opinion of the Review Team it is unusual to have four meetings per month given the review volume at the HREB. However, the Review Team cautions against reducing the frequency of meetings until the observations identified in Objective One are addressed.

OBJECTIVES THREE AND FOUR:

Governance, Reporting & Accountability and Roles: REB, REB Office (REO) and REB Chairs

Objectives 3 and 4 have been addressed together in this section as governance (Objective 4) provides the framework for REB/REO accountability and REO staff roles and reporting.

Environmental Scan

REB Governance

In academic/hospital settings the responsibility for ethical oversight is delegated to a REB(s) by the highest authority within that institution, for example the Board of Directors or the Board of Trustees. The institution can designate one or multiple REBs to review research on its behalf. In the academic/hospital setting the REB most often reports to this highest authority through another committee, examples of which include medical advisory, quality and safety, academic advisory or research committees. The REB may also report directly to the Board of Directors of the institution, but it is most common for there to be an intermediary committee or body more closely connected to patient care and/or research.

In one case a disease specific provincial REB housed within a research organization reports to a Governance Committee established by the organization. The Governance Committee reports to the Organization's Board of Directors. The role of the Governance Committee is to ensure the independence of the ethics decision and ensure the quality of ethics reviews.

For another provincial REB the REB reports directly to the CEO of the research organization that houses the REB.

Information regarding Governance in Private REBs could not be obtained. It is expected that in most cases private REBs do not report to a "higher authority" such as a governance committee or board of directors; however, they are typically accredited by a credible outside body [e.g., Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP)].

Reporting & Accountability

In academic/hospital settings, most commonly, REO personnel report to a REB Manager/Director. The REB Manager/Director typically reports along corporate lines to a senior administrator within the organization's Research Administration portfolio (i.e., Director - Research Operations, VP Research or similar).

In the case of the two provincial REBs the Directors reported to senior corporate leadership of the institution, and REB staff report to the Directors.

In a few cases the REB Chair will have a direct or administrative reporting responsibility to an individual within the institution/organization. Individuals they may report to include Physician-in-Chief, VP Research, or the CEO of the host institution. In many cases a direct or administrative reporting line is not defined specifically for the REB Chair, rather the "REB" as an entity reports to a higher authority.

Roles

In general, the key responsibilities of REO personnel are consistent amongst REBs. Common roles and responsibilities are outlined in the table presented here:

Role	Common Responsibilities
REB Chair	• Ensuring that the REB review process conforms to the requirements of TCPS 2 • Providing overall leadership for the REB and facilitate the REB review processes, based on institutional policies and procedures • Monitoring the REB's decisions for consistency and ensuring that decisions are recorded accurately and communicated clearly in writing as soon as possible by the Chair or their designate [TCPS 2 (2014) Article 6.8]
Manager/Director	• Assessing resources, hiring and terminating REO personnel, and performance evaluation of REO personnel (in accordance with organizational policies) • Ensuring the review process is operating efficiently and effectively • Understanding the various regulations, policies and guidelines that apply to research ethics and supporting conformity by way of Standard Operating Procedures, guidance documents and templates • Liaising with the REB and Institution to resolve challenges
Ethics Coordinator/ Ethics Officer	• Day-to-day administrative processing of ethics applications, including screening activities, corresponding with the research team, sending applications to the REB/REB Chair for review • Liaising with the Research Ethics Manager/Director or REB Chair for guidance as needed • At some REBs, the Coordinator conducts delegated reviews on behalf of the REB subject to regulatory/policy requirements
Administrative Assistant	• Vary based on the number and role of other REO personnel • Preparing REB meeting agendas and review packages • Triaging emails/calls to other REO personnel • Filing, scanning and data entry

HREB

Governance

In Newfoundland and Labrador the Health Research Ethics Authority (HREA) is an independent corporation and has the authority to ensure health research involving human subjects is conducted in an ethical manner. The HREA is required to appoint the Health Research Ethics Board (HREB) respecting

the principles outlined in the TCPS. The corporation has 4 directors appointed by the Minister. The directors represent Memorial University, the Eastern Regional Health Authority, the Ministry and the public.

The only reference to a formal reporting relationship between the HREA and HREB is found in the HREB Terms of Reference and states the HREB will provide an annual report to the HREA. The Review Team was informed that these annual reports have not been done historically, but one was requested by the HREA this year.

Reporting and Accountability

All REO personnel are employed by Memorial University (MUN). The Receptionist, Secretaries, and Ethics Officer report to the Ethics Director.

The Ethics Director reports to the HREA by way of monthly meetings with the HREA Board of Directors. At these meetings, the Ethics Director provides a "Director Report" which includes progress updates on HREA goals and highlights of staff activity, recruitment outcomes, and Committee work. Metrics are beginning to be presented monthly and include:

- number of applications per fiscal year per each REB
- length of time to final decision (average, median and range) per each REB
- time spent at Board (average, median) per each REB
- time spent with researcher (average, median) per each REB
- number approved, number rejected, number withdrawn
- number of open trials
- number of amendments and time to approval
- number of annual renewals

There is no formal evaluation of the Ethics Director by the HREA.

There are no personal performance contracts or reporting requirements of the HREB Chairs to the HREA.

The key roles and responsibilities of the REO team are presented here:

Role	Key Activities
Receptionist (1)	• Prepare and send out correspondence • Preparing and distributing ethics renewal notifications, tracking renewal applications for non-responders, generate closed file reminders on a monthly basis • Acknowledging receipt of applications from Investigators • Assigning reference numbers to applications • Composing lists (approvals, renewals, closed files, expedited review) for HREB meetings • Maintain office databases(s), generate reports from the databases • Assist in preparation of meeting materials and agenda packages for the HREB meetings • Answering telephone/in-person inquiries

Secretary to the HREB – Clinical Trial Subcommittee (HREB-CT) (1) Secretary to the HREB – Non-Clinical Trial Subcommittee (HREB-NCT) (1)	• Coordination of daily activities with the Chair/Co-Chair and Ethics Officer • Preparing and sending correspondence • Screening of submissions for appropriate information • Liaising with researchers and research staff on the direction of the EO • Compiling agenda packages, and taking and transcribing HREB meeting minutes
Ethics Officer (EO) (1)	• Supporting the work of the HREBs • Coordinating the work of the ethics office staff • Managing the HREB application process • Provides expertise in research ethics board operations and conduct of health research and ensures compliance with applicable regulations, policies and standards. • Acts as a liaison – providing information and assistance - to researchers, the HREBs, research staff, sponsors and regulators; and communicates concerns, complaints and breaches to the appropriate contacts • Education of orientation and education activities for members of the HREBs and other stakeholders
Ethics Director (1)	• Supporting the work of the HREBs • Coordinating the work of the ethics office staff • Leads the implementation, maintenance and continued improvement of the provincial research ethics review process • Contributes significantly to HREA strategic planning, resource planning and the development of the sustainability of the ethics review process • Responsible for monitoring of health research and other oversight initiatives. • Develops and implements education to support a province-wide research ethics review process • Develops and implements HREA policies and procedures and other tools necessary to ensure effective governance of health research ethics in the province. • Manages the financial activities of the Ethics Office and the HREA • Leads outreach and engagement for the HREA, works closely with stakeholders in NL and research communities to understand the environment for the REB review of health research

Discussion

As stated in the TCPS, "A key goal in establishing an appropriate governance structure for research ethics review is to ensure that REBs operate with a clear mandate, authority and accountability; and that roles and responsibilities are clearly defined" (p. 69). Additionally, each institution is accountable for the research carried out in its jurisdiction or under its auspices (Article 6.1, Application) and is responsible for providing appropriate administrative resources "for the effective and efficient operation of the REB" (Article 6.2, Application).

The TCPS requires the highest body in each institution to establish or appoint an REB(s) to review the ethical acceptability of the research and to establish the necessary structure of the REB (Article 6.1, P.69 and Article 6.2, p.70). The institution must:

- establish the necessary structure for the REB(s),
- define an appropriate reporting relationship,
- grant the REB the mandate to review the ethical acceptability of research on behalf of institution (Article 6.3),
- respect the authority delegated to the REB and not override an REB decision to reject a research proposal,
- ensure REBs are independent in their decision making and are accountable to the highest body that established them for the process of research ethics review, and
- have in place written procedures for the appointment, renewal and removal of REB members, including Chairs.

Institutions should have clear policy and procedures documenting how the REB(s) is governed and how compliance with the TCPS requirements noted above is achieved. Similarly, the institutions relying on the HREB should have policy that address the requirements above, or clearly establish delegation of appropriate duties to the HREA/HREB. Additionally, the HREA/HREB should have written policies and effective procedures that support the above TCPS requirements that are delegated by the institutions relying on the HREB.

Although governance models and reporting lines vary slightly, the models examined here to do not differ substantially and all have the potential to support high quality and efficient ethical review. Here the Review Team presents potential benefits and challenges with different models; however, it is emphasized that with adequate clarity in governance, policy/procedures, responsibilities and reporting—as well as effective supports and communication—any of the models can work well and be compliant with the TCPS.

<u>Institutionally Based REBs</u>

It is most common for REBs to be established by institutions conducting research. As noted above, such institutional REBs typically report to the highest authority within the institution and in most cases this occurs through a committee responsible for research and/or patient care. The senior REO staff member (Manager/Director) will have a clear reporting line to an individual in the institution and typically the person to whom they report has responsibilities for the research enterprise (VP Research or Director – Research Operations). The REO personnel (through the senior REO staff member) and the REO senior

staff member are accountable to the institution, which is accountable for all research carried out under its auspices.

Potential benefits of this model are:

- The REB is responsible for ensuring the ethical acceptability of research (TCPS2), whereas the institution is responsible overall for the research conducted under its auspices. Reporting to the highest authority can help to ensure the REB is independent in its ethical decision making, while the corporate reporting line of the REO leadership can help to ensure the institution meets its oversight obligations, provides high-quality supports to the research community, and is aware of and can manage any institutional liabilities related to ethical review and the ethical conduct of research.
- By reporting through a committee responsible for research and/or patient care, the performance of the REB and REO is contextualized through related operations of the institution. This also supports clear reporting requirements and independence between the REB and REO, and the highest body to which it reports.
- Academic institutions/hospitals have the infrastructure and expertise to support and govern activities, employees and volunteers across a broad range of research related activities and ensure all align with the mission and values of the organization.
- Researchers with concerns about the REO processes or REB are typically members of the institution housing the REB and may have more direct lines for reporting and resolving issues.

Challenges with institutionally based REBs can be the following:

- Management of conflict of interests; the institution's desire to advance research may appear to or conflict with its responsibility to ensure high quality ethical review.
- As one of many supports for research within the institution, the REB is subject to resource availability and institutional decisions around allocation of resources.

<u>HREB</u>

The HREB has been established by the HREA, an independent corporation with the authority to ensure health research involving human subjects is conducted in an ethical manner and the requirement to appoint the HREB.

Benefits of this model and how it has been implemented in Newfoundland and Labrador are as follows:

- As an independent corporation the HREA is further removed from institutional research or other institutional priorities
- The HREA is supported by the provincial Health Research Ethics Authority Act which signifies the importance of the ethical review of research for participants in Newfoundland and Labrador
- The HREB structure provides a single REB for all health-related research in Newfoundland and Labrador, providing consistency and a high potential for quality and efficiency in the ethical review of research across the province

The challenges of this model and how it has been implemented in Newfoundland and Labrador are as follows:

- As an independent corporation the HREA's connection and responsibility to the research community are limited, compared to academic institutions/hospitals.
- Researchers lack an effective mechanism for addressing concerns with the REB and REO processes and personnel.
- The reporting mechanism of the REO to the HREA is unclear and insufficiently documented.
- As a governing entity the HREA lacks independence from the operational arm of the HREB, with the Ethics Director engaging substantially in both HREA and HREB activities and attending HREA meetings.
- The Ethics Director is not adequately supported or supervised through performance reviews, performance expectations and a clear reporting relationship.
- It is unclear if the REB chairs have oversight, reporting responsibilities or support with respect to serving in this role.
- REB members expressed a lack of engagement and communication from the HREA. Areas of concern included the implementation of an REB user survey by the HREA without the knowledge of the HREB, a lack of recognition and appreciation by the HREA for the work of the HREB members (volunteers), and a lack of clarity regarding the role of the HREA.
- Aspects of the Health Research Ethics Authority Act differ from the requirements of the TCPS 2 (appeals, for example). Further, the REB is considered a 'quasi-judicial body' and becomes subject to legal considerations that do not normally govern research ethics review and are not necessarily consistent with the requirements of the TCPS. These differences may not be understood within the usual research ethics framework and may require additional resource at the HREA or REO and present challenges to all involved in the research endeavour.
- Institutions/organizations who are conducting clinical trials or genetic research are unable to delegate research ethics oversight to any other REB. This may put the province at a disadvantage when it comes to multi-centre clinical trials in particular. TCPS 2 (Chapter 8) recognizes different review mechanisms for research involving multiple institutions and/or REBs

Provincial REBs

The REBs reviewed were similar to the HREB in that they are established by and report to an organization outside of academic/hospital environment. This potentially provides more independence but as for the HREB may provide less connection to the research community as what is seen with institutionally based REBs. The chairs of these boards directly report to a Governance Committee in one case, and the CEO of the organization in the other.

Recommendations

The Review Team recommends the following with respect to governance, roles and reporting responsibilities:

- The HREA foster stronger relationships with the institutions and organizations relying on the HREB for review and establish clear and effective mechanisms for regularly seeking input and receiving and resolving complaints from the research community; collaborate with these institutions/organization to develop educational or other supports for research teams to improve the quality of ethics submissions

- The HREA develop clear policy and procedures to support oversight of the HREB and REO with respect to effective and efficient operations, while ensuring the HREB is independent in its ethical decision making. Measures to consider include:
    - The development of clear policy and procedure, consistent with the TCPS, outlining the roles and responsibilities and reporting requirements of the HREA, HREB, REB Chair(s) and REO personnel. Close collaboration with the institutions relying on the HREB for ethics review is recommended when developing such policies and procedures.
    - The HREA (in conjunction with MUN and other organizations as applicable) establish a formal process for reporting and managing concerns related to the performance of REO personnel, and for addressing REO personnel concerns regarding researcher conduct. This recommendation is intended to support both the REO personnel and researchers by way of establishing independent, fair, transparent and timely procedures.
    - The leadership of the REO be dedicated to supporting the REB and the research community. This position can continue to report to the HREA with respect to HREB/REO Operations but should not regularly attend HREA Board of Director meetings
    - The HREA should ensure that performance management processes apply to all members of the REO.
    - The HREA convene the constituent committee as described in the Act or a similar body with a strong understanding of research, research ethics, health care and patient/participant issues. Such a committee could provide valuable expertise and insight to the Directors of the HREA as well as connection to the communities the HREA serves.
    - The HREA/HREB review the membership of the HREB to ensure it is representative of the research community. Consideration to expanding the membership to include research nurses and Clinical Research Associates (CRA) should be given. Alternate and shared membership positions would help to achieve and maintain quorum.
    - The HREA develop measures for supporting and recognizing the contribution of HREB Chairs and members. It is recognized that the Act insists on members of the board being unpaid; however, especially with respect to REB Chairs remuneration, or consideration in the form of relief of other duties, is common place. This is especially the case when REBs are not institutionally based. Note Article 7.3, TCPS2 “Reasonable compensation by institutions for work done by REB members is appropriate. However, in some instances, individual members of the REB may have a conflict of interest in accepting undue or excessive honoraria for their participation in the REB. Institutions should define appropriate levels of compensation.”

APPENDIX 1: METHODOLOGY

Objective One

Pre-Visit Activities

During the pre-visit period, the Review Team worked with the HREA to finalize the review plan and scope of studies for review.

The Pre-visit Questionnaire was provided to the REO; the completed questionnaire and associated materials were received on July 15, 2018:

- **Position descriptions of all office staff involved in the research ethics review process**
- **Workflow diagram**
- **HREB clinical trial application forms**
    - HREB Clinical Trial Application Form – Part A
    - HREB Clinical Trial Application Form – Part B
- **HREB clinical trial event reporting forms**
    - Personnel Change Notification Form
    - Amendment Form
    - Investigator Brochure Reporting Form
    - Product Monograph Reporting Form
    - Request for Ethics Renewal/Study Closure
    - Safety Reporting Form
    - Serious Adverse Event Reporting Form – Local Event
    - Funding Source/Sponsor and/or Partner Change Notification Form
- **HREB clinical trial guidance documents**
    - Guidance Notes for Researchers re: the Submission of a Clinical Trial
    - Guidelines for Consent for Research
    - Guidelines for Completing HREB Clinical Trial Applications
    - Patient Engagement and Research Ethics Guidelines
- **Informed consent form templates**
    - Consent to take part in a clinical trial
    - Clinical Trial Optional/Substudy Consent Form
    - Pregnancy Follow up Consent
    - Optional Consent Form sections
    - A letter of new information (consent addendum)
- **Checklists applicable to the HREB clinical trials committee**
    - REB Quick Reference Checklist – Aboriginal Peoples
    - REB Quick Reference Checklist – Consent
    - REB Quick Reference Checklist – Justice
    - REB Quick Reference Checklist – Privacy
    - REB Quick Reference Checklist – Biomaterials
    - REB Quick Reference Checklist – Human Genetics
    - REB Quick Reference Checklist – COI
    - REB Quick Reference Checklist – Children
    - REB Quick Reference Checklist – Disaster Situations
    - REB Quick Reference Checklist – Placebos

- **Available metrics**
    - 2016 calendar year metrics
    - 2017 calendar year metrics

The following documents were obtained from the HREB website (http://www.hrea.ca/HREB.aspx):

- HREB Terms of Reference dated June 2016
- HREB Policy Manual dated March 27, 2012
- HREB Policy on Re-opening Closed Files

On June 26, 2018, the REO contacted clinical trial investigators, inviting participation in interviews with the Review Team.

On-Site Review Preparation Meeting

A preparation meeting was held on June 26 to discuss the HREB Clinical Trials Committee operational procedures (including intake process) and the roles and responsibilities of the operations team.

On-Site Review

The on-site review occurred June 27-28, 2018. The on-site review included interviews with HREA, REO personnel, HREB members and Investigators. In addition, the Review Team had access to 5 pre-selected studies (studies identified pre-visit by the REO as representing the shortest, longest and average review times), redacted meeting agenda and minutes for the previous 6 months, and the redacted meeting agenda and minutes for the pre-selected studies. The Review Team was also provided with the HREB Event Decision Making Table and the results of a survey conducted in 2017 entitled "2017 HREB Feedback Form for Researchers and Research Team Members".

Post-Visit Follow-up

Additional Investigator interviews were held by phone on July 5 and 6, 2018.

Following the on-site review, the REO invited the HREB Clinical Trial Committee members to participate in an interview with the Review Team. The Review Team conducted two additional interviews as a result of this outreach.

The Review Team obtained study files for 9 additional pre-selected studies.

Comparator Studies

The 2017 approved study information (provided in the 2017 calendar year metrics) was reviewed to determine which of the clinical trials were multi-centre and involve other academic/institutional REBs in Canada using clinicaltrials.gov data. Based on this review, 7 studies were identified as potential 'comparator' studies. The Review Team had access to the records for 5 of these studies from the pre-selected study set, and the study files for 2 additional studies were obtained.

Where possible, the Review Team used the data in clinicaltrials.gov to predict the likely REB of Record for the clinical trial site and requested information from the REB of Record. REBs agreeing to participate in the process were asked to provide review timeline information and general overview of ethical issues (if applicable) for those comparator studies they reviewed.

Objective Two

Data from the Pre-visit Questionnaire and supporting documentation obtained from Objective One was used for assessment of the HREB Clinical Trial (CT) committee. The 'Objective Two' Questionnaire and supporting documentation was used to obtain information on workload and resources for the HREB Non-Clinical Trial (NCT) committee.

Publicly available data were limited and insufficient to identify REBs of similar volume or timeline data for comparison as anticipated. As a result, CTO reviewed data internal to CTO for information on REO resourcing.

Similar REO job titles are represented by the most title/name to ensure anonymity.

Objectives Three and Four

Information on reporting and accountability structures of the HREB and REO was requested via the Objective Three Questionnaire. Comparator REB information was obtained from CTO REB information on file, accessing public records, and contacting REBs for additional information as appropriate.

PRE-VISIT QUESTIONNAIRE

HREB Clinical Trials Committee

SECTION 1 - General Information

Please provide a list of individuals working with the HREB Clinical Trials Committee (e.g., HREB Operations Personnel, HREA staff), their roles and responsibilities:

Click to enter text.

SECTION 2 – Materials for Pre-Review

Please provide the following documents as part of the pre-review package:

1. HREB Terms of Reference:

Enclosed ☐ Not Available ☐ OR
Publicly Available: Click to enter link to online version if applicable.

2. Standard Operating Procedures:

☐ Option 1: Enclosed

☐ Option 2: Publicly available. Please provide website link:

Click to enter link to online version if applicable.

3. Workflow diagrams:

Enclosed ☐ Not Available ☐ OR
Publicly Available: Click to enter link to online version if applicable.

4. HREB Clinical Trials Committee Application forms (Initial submission, Amendments, Continuing Review, Unanticipated Problems):

☐ Option 1: Enclosed

☐ Option 2: Publicly available. Please provide website link:

Click to enter link to online version if applicable.

5. Guidance and process documents:

Enclosed ☐ Not Available ☐ OR
Publicly Available: Click to enter link to online version if applicable.

6. Informed Consent form template(s) applicable to the HREB Clinical Trials Committee

Enclosed ☐ Not Available ☐ OR

Publicly Available: Click to enter link to online version if applicable.

7. Other templates and checklists applicable to the HREB Clinical Trials Committee

Enclosed ☐ Not Available ☐ OR

Publicly Available: Click to enter link to online version if applicable.

8. Available metrics:

Enclosed ☐ Not Available ☐ OR

Publicly Available: Click to enter link to online version if applicable.

Are any SOPs under revision or currently being developed and have not been submitted?

☐ Yes ☐ No

If yes, please list the titles of these SOPs and the expected completion date:

Click to enter text.

SECTION 6 - Research Reviewed by the HREB Clinical Trials Committee

Please estimate how many reviews the HREB Clinical Trials Committee conducts annually in each of the categories:

Click to enter # Initial Reviews

Approximately how many of these are clinical trials? Click to enter #

Approximately how many of these are multi-centre clinical trials? Click to enter #

Click to enter # Amendments

Click to enter # Continuing Reviews/ Renewals

Click to enter # Reportable Events (unanticipated problems, deviations, etc.)

How many studies (total) are currently approved and require ongoing review by the HREB Clinical Trials Committee?

Click to enter #

(i) How many of these are clinical trials? Click to enter #

(ii) How many of these are multi-centre studies? Click to enter #

Please provide a brief description of any metrics collected by the HREB Clinical Trials Committee (e.g., time from meeting to letter issuance, etc.):

Click to enter text.

OBJECTIVE TWO QUESTIONNAIRE

HREB Non-Clinical Trial Committee
SECTION 1 - General Information
Please provide a list of individuals working with the HREB Non-Clinical Trials Committee (e.g., HREB Operations Personnel, HREA staff), their roles and responsibilities, and their employer (e.g., HREA, MUN, etc.): Click to enter text.
SECTION 2 - Research Reviewed by the HREB Non-Clinical Trials Committee
Please estimate how many reviews the HREB Non-Clinical Trials Committee conducts annually in each of the categories: Click to enter # Initial Reviews Click to enter # Amendments Click to enter # Continuing Reviews/ Renewals Click to enter # Reportable Events (unanticipated problems, deviations, etc.)
How many studies (total) are currently approved and require ongoing review by the HREB Non-Clinical Trials Committee? Click to enter #
Please provide a brief description of any metrics collected by the HREB Non-Clinical Trials Committee (e.g., time from meeting to letter issuance, etc.), if different than the metrics previously provided for the Clinical Trials Committee: Click to enter text.

HREB Non-Clinical Trial Committee
SECTION 1 - General Information
Please provide the employer for the roles listed below (i.e., to supplement the information in the Pre-Review Questionnaire previously submitted for the CT Committee), if not covered in Section 1 above:

Receptionist: Click to enter text.

Secretary to the HREB – Clinical Trial Subcommittee (HREB-CT): Click to enter text.

Ethics Officer: Click to enter text.

Ethics Director: Click to enter text.

OBJECTIVE THREE QUESTIONNAIRE

HREB CT and NCT Committee
Please describe the reporting relationship between the HREB and the HREA: Click to enter text.
Please describe HREB accountability mechanism(s) with the HREA and/or sites for which it provides research ethics review (e.g., annual reports, newsletters, etc.): Click to enter text.
Research Ethics Office
Please describe the reporting between the Research Ethics Office and the HREA and/or HREB and/or sites for which it provides research ethics review: Click to enter text.
Please describe Research Ethics Office accountability mechanisms with the HREA and/or HREB and/or sites for which it provides research ethics review: Click to enter text.
Organizational Chart
If available, please provide an organizational chart(s) depicting the reporting relationships of the HREB and the Research Ethics Office Enclosed ☐ Not Available ☐

APPENDIX 2: REFERENCES

[i] Office of the Information and Privacy Commissioner, Disclosure of Personal Health Information for Research Purposes: Guidance for Researchers and Custodians of Personal Health Information (September 11, 2017). Accessed from: https://www.oipc.nl.ca/pdfs/disclosure_personal_health_info.pdf

[ii] Canadian Association of Research Ethics Boards (CAREB), Guidance on Reporting of Unanticipated Problems Including Adverse Events to Research Ethics Boards in Canada (2010). Accessed from: https://www.careb-accer.org/sites/default/files/downloads/careb_guidance_-_ae_reporting_-_july_2010.pdf

[iii] University of British Columbia (UBC), Guidance Note #18 : Special Categories of Research-Research Involving Human Biological Materials (May 2016). Accessed from: https://ethics.research.ubc.ca/sites/ore.ubc.ca/files/documents/UBC%20Guidance%20Note%20Human%20Biological%20Materials%20May%202016.pdf

[iv] Ontario Cancer Research Ethics Board (OCREB), OCREB Optional Consent Form Template (May 23, 2017). Accessed from: https://oicr.on.ca/wp-content/uploads/2017/12/OCREB_-Optional_-Consent_Form_Templatev2017-May-23.docx