Pilot Model for Harmonization of Clinical Trials

SCOPE

1. The scope of this document applies to clinical trials conducted under the auspices of more than one Research Ethics BC (REBC) partner institution and includes:
    a. Trials in which the lead principal investigator/sponsor is conducting the trial under the auspices of a REBC partner institution;
    b. Minimal risk and above-minimal risk trials;
    c. Health Canada regulated and non-regulated trials;
    d. All clinical trial designs, including pilot & feasibility trials in which an intervention is administered; long-term extension studies are included; AND,
    e. Interventions may include (but are not limited to) drug administration, medical devices, natural health product administration, surgical procedures, telehealth, non-invasive interventions and techniques including psychological, eHealth and rehabilitation interventions, imaging procedures, etc.
2. Excluded from this pilot are trials that are sponsored by a corporate/industry/for-profit entity, and/or where the trial data is sent to a corporate/industry/for-profit entity.
3. This guidance is intended as further clarification to the existing minimal risk/above minimal risk harmonized ethical review models. Not all sections will be applicable to all trials.

DEFINITIONS

4. Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioural health-related outcomes.
5. Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial (ICH E6 (R2), 1.53)
6. Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator (ICH E6 (R2), 1.54). Also referred to as the "lead Principal Investigator".
7. Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator or site principal investigator (ICH E6 (R2), 1.34). Also referred to as "Principal Investigator".
8. Qualified Investigator: The person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is: a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional

medical or dental association; and b) in any other case, a physician and a member in good standing of a professional medical association (Health Canada Food and Drug Regulations Part C, Division 5, Section C.05.001)

9. Sub-Investigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (ICH E6 (R2) 1.56)
10. Co-Investigator: Any individual member of the study team who makes a significant contribution to the intellectual direction of the research or research-related activity, who plays a significant role in the conduct of the research or research-related activity, and who may also have some responsibility for financial aspects of the research. The term "co-investigator" is used to designate study team members for non-regulated clinical trials, whereas "sub-investigator" is used for regulated clinical trials.
11. Home Institution: The institution with whom the Principal Investigator has a primary appointment and under whose auspice the research is being conducted.
12. Minimal Risk: 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 the aspects of their everyday life that relate to the research (TCPS 2)
13. Above Minimal Risk: Research in which the probability or magnitude of possible harms implied by participation in the research is greater than those encountered by participants in the aspects of their everyday life that relate to the research (TCPS 2)
14. Serious Adverse Events (SAEs): Any untoward medical occurrence that: 1) results in death; 2) is life-threatening; 3) requires inpatient hospitalization or prolongation of existing hospitalization; 4) results in persistent or significant disability/incapacity; 5) is a congenital anomaly/birth defect; based upon appropriate medical judgement, is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above. Local serious adverse events that are unexpected and related or possibly related to the trial, including Serious Unexpected Adverse Drug Reactions (SUADRs) and Medical Device Serious Adverse Events (MDSAEs) must be reported to the BoR.

INITIAL APPLICATION

1. Lead Principal Investigator (PI) submits initial ethics application on the PREP system.
    a. PREP system will determine the appropriate REB to serve as BoR.
    b. REB administrator may consult with relevant partner REBs to determine appropriate Board of Record (BoR) if there is disagreement over the PREP-assigned BoR.
    c. The BoR determines if the appropriate application form (behavioural or clinical) is used, and may request that the PI revise the application form accordingly.
2. Lead Principal Investigator identifies sites & Qualified Investigators (QIs)/Site PIs for each site in which the intervention is being administered in initial ethics applications.
    a. Site PIs must be listed on PREP Section 1.3 with their appropriate institutional affiliation, as it relates to the trial. For regulated trials, the site QIs must be given online access to the application.

   b. If site-specific PIs and/or QIs for all applicable sites are not identified, the application is returned to the lead PI as an incomplete application.
   c. Clinical trials registration number is submitted, as applicable.
   d. Health Canada Letter of No Objection, Investigational Testing Authorization and/or Notice of Authorization is submitted, as applicable.
   e. Data Safety Monitoring Plan is included in the protocol (as applicable).
   f. Sponsor/funder is clearly identified.

3. Lead PI ensures that information for all the identified sites covered under this harmonized REB review is included in this application. The list below identifies key aspects of the application where site specific information may be needed; however it is not necessarily an inclusive list, so whether site-specific information is needed should be considered throughout the application.
   a. Co-Investigators – All site PIs/QIs and site co-investigators/sub-investigators must be listed on the application (Section 1.3) as co-investigators to ensure they are appropriately listed on the Certificate of Approval.
   b. Site PI's/QI's CVs may be required.
   c. List all sites involved – including the names of the health authority (if applicable) and each site within each health authority.
   d. Recruitment – describe the recruitment methods for participants and normals/controls (if applicable), including all site-specific information, if there are any differences in approaches to recruitment across sites.
   e. Consent – describe the consenting process and include all site-specific information, if there are differences in approaches to consent across sites.
   f. List the total number of anticipated participants across the study.
   g. List the total number of anticipated participants at each site.
   h. Data and record management/security detailed for each site.
   i. Consent forms are site specific for above minimal risk interventional studies, with identified qualified investigators and local emergency numbers identified.
   j. List the payment per site, if applicable or attach the budget (often a 'Schedule A' or attachment to the agreement between the funder and the lead PI)
4. BoR conducts pre-review to ensure the above requirements are met (If not, the application should be returned to the PI for completeness) and determines level of review, as per the REB's normal process.
5. For Minimal Risk, delegated reviews, the BoR reviews the study as per normal process. Once initial review is complete, the partner REBs are provided with the initial review and study documents in order to conduct site-specific reviews as needed.
6. For Above Minimal Risk, full-board reviews, the BoR must harmonize the file on **RISe 7 to 10 business days** prior to the meeting to permit sufficient review time. Partner REBs are invited to send a member to the meeting in person/by phone. Other reasonable accommodations can be made on a case-by-case basis.
   a. Quorum must meet the TCPS 2 requirements, including: standards:
      - At least two members who have relevant knowledge and expertise in the content area

- At least one member who is knowledgeable in ethics
- At least one member who is knowledgeable in the relevant law
- At least one member who has no affiliation with the institution, but is also recruited from the community

b. Quorum is based on who is present at the meeting (physically and remotely). This includes designated members of other REBs who participate in the collaborative review. In the event of a vote, the designated members of the other REBs are entitled to vote

c. Attendees who are voting members of their own REB will be considered voting members in the same capacity they serve in their own REBs to meet the quorum

7. Participating REBs must indicate whether they request to review the response to provisos (if applicable) or to delegate this responsibility the BoR on their behalf.
8. The BoR compiles the reviews of all partner REBs and distributes to the PI via the PREP system.

CERTIFICATE OF APPROVAL

1. When all provisos have been satisfied, the BoR issue a Certificate of Approval (CoA).
2. Partner REBs will be notified of the approval via the PREP automatic notification system.
3. The lead PI is responsible for ensuring site PIs receive copies of all Certificates of Approval.

ACKNOWLEDGEMENT REQUESTS (i.e., DSMB reports, Administrative letters, IB updates, etc.)

1. The lead PI submits all requests for acknowledgement to the BoR for review.
2. The BoR will issue the acknowledgement to the PI. Partner REBs will be notified of the acknowledgement via the PREP automatic notification system.
3. Where material changes to the study are requested in light of acknowledgement submissions, the partner REBs will be provided an opportunity to comment prior to the issuing of an acknowledgement to the lead PI.
4. External/Non-Local Adverse events should be first analyzed by the sponsor and/or data and safety monitoring committee to assess whether it constitutes an “unanticipated problem”. These events should be reported in a periodic safety update report prepared by the sponsor/PI. Individual isolated external adverse events should only be reported to the BoR if they are unanticipated problems and the report includes all of the following information:
    a. The event described is both serious and unexpected,
    b. The report identifies all previous safety reports concerning similar adverse experiences,
    c. The report analyzes the significance of the current adverse experience in light of the previous reports, and
    d. The report outlines any proposed protocol changes, informed consent form changes or other corrective actions to be taken by the sponsor in response to the unanticipated problem
5. Any unanticipated serious adverse events occurring at one of the participating sites covered by the harmonized ethical review should be submitted as a Local SAE, rather than an External/Non-Local SAE, by the site PI using the PREP system.

REPORTABLE SERIOUS ADVERSE EVENTS

1. Lead PI or site PI must submit the PAA within **15 calendar days** of the investigator becoming away of the problem(s). Fatal or life-threatening reportable local SAEs should be reported within **7 calendar days.**
2. BoR will notify the applicable site PI's REB within **2 business days**.
3. Site PI's REB will review the SAE submission, and request additional information if required from the site PI as required, and the site PI's REB will upload any additional information on the PREP file as required.
4. If corrective actions/substantive changes to the study are requested by the site PI's REB (e.g., changes to the consent form, additional reporting, etc.), these changes will be presented to the lead PI's REB for discussion on a case-by-case basis.

PROTOCOL DEVIATIONS & OTHER UNANTICIPATED PROBLEMS

1. Lead PI or site PI submits the protocol deviation report to the PREP file within **15 calendar days of discovery.**
    a. Deviations or changes form the protocol to eliminate immediate hazards to participants must be reported to the PREP file as soon as reasonably possible, but not more than within **5 days** of discovery.
2. BoR will notify any impacted site PI's REB within **2 business days.**
3. Site PI's REB will review the protocol deviation submission, and request additional information from the site PI as required; the site PI's REB will upload any additional information as required.
4. If corrective actions/substantive changes to the study are requested by the site PI's REB (e.g., changes to the consent form, additional reporting, etc.), these changes will be presented to the lead PI's REB for discussion on a case-by-case basis.
5. Any privacy breaches should addressed in accordance with local privacy policy requirements of the institutions impacted directly by the breach.
6. Site PI's REB will review the protocol deviation submission and request additional information if required from the site PI as required; the site PI's REB will upload any additional information as required.
7. If corrective actions/substantive changes to the overall study protocol or supporting documents are requested by the site PI's REB (e.g., changes to the consent form, additional reporting, etc.), these changes will be presented to the lead PI's REB for discussion on a case-by-case basis.

AMENDMENTS

1. Site PIs may submit minor administrative amendments that do not impact study documentation (e.g., consent forms, recruitment posters, etc.). The lead PI will submit all other amendment requests, regardless of whether they are site-specific or apply to the overall study.
2. The BoR will pre-review the amendment as per their normal process to determine the level of review.
3. For minimal risk amendments qualifying for delegated review, the BoR will determine on a case-by-case basis whether the proposed changes are substantive and require notification to partner REBs

for review, or whether the proposed changes are non-substantive and do not require review by partner REBs.

   a. Substantive changes: the BoR will review as per normal process and forward the study documents and review to partner REBs for site-specific review. Partner REBs accept direct reciprocity of BoR's review, or choose to partake in the review. If they choose to review, they must indicate whether they will review the response to provisos or will delegate this responsibility to the BoR, as required.
   b. Non-substantive changes: the BoR will review as per normal process. Once approved, the approval certificate will be issued via the PREP system.

4. For amendments requiring full board review, the BoR will notify the partner REBs, and distribute the study documents, including the pre-review seven days before the full board meeting.
   a. Partner REBs are invited to send a member to the meeting in person/by phone, or to submit site specific comments for review prior to the meeting, or within three days after the meeting.
   b. The BoR will provide meeting minutes to the partner REBs.
   c. Participating REBs must indicate whether they require to review the response to provisos (if applicable) or to delegate this responsibility to the BoR on their behalf.
   d. For amendments that require Health Canada approval, the updated No Objection Letter must be included in the amendment submission.
5. The BoR compiles the review of all partner REB provisos and distributes to the lead PI as per normal process.
6. Once approved, the BoR will issue the approval certificate via the PREP system.

RENEWALS

1. Lead PI submits annual renewal to the BoR as per normal process.
2. The BoR pre-reviews the renewal application to determine the level of review.
3. For renewal applications qualifying for delegated review, the BoR will review and approve as per normal process.
4. Renewal applications should include the following information[1]:
   - Number of participants enrolled at each site
   - Number of participant withdrawals
   - Number of participant complaints
5. For renewal applications requiring full board review, as requested by the Principal Investigator or determined necessary by the BoR Chair, the BoR will notify the partner REBs, and distribute the study documents, including the pre-review seven days before the full board meeting.
   a. Partner REBs are invited to send a member to the meeting in person/by phone, or to submit site specific comments for review prior to the meeting, or within three days after the meeting.
   b. The BoR will provide meeting minutes to the partner REBs.

[1] The Renewal Application in RISe will be assessed to determine if modification is required to accommodate this information being collected

   c. Participating REBs must indicate whether they require to review the response to provisos (if applicable) or to delegate this responsibility to the BoR on their behalf.
6. If partner REBs wish to be included in the review of a particular renewal application, it is the responsibility of the partner REB to make this request to the BoR.
7. Once approved, the BoR will issue the approval certificate via the PREP system.

CLOSE OUTS

1. For study-wide closure: Lead PI submits the close-out application to the BoR. The BoR reviews the application as per normal process, and will inform the partner REBs of the study closure. Partner REBs will ensure that administrative requirements related to the study closure are completed by the research team. Once all requirements are met, the BoR sends the acknowledgment to the lead PI and partner REBs.
2. For site-specific close-outs: Site PI submits the site specific close-out as an amendment to the BoR. The BoR will notify the affected REB(s) and facilitate documentation of site closure activities.

STUDY TERMINATION

1. Termination of a study or study site by the REB requires collaborative discussion between BoR and relevant partner REBs and will require a case-by-case approach.

STUDY MONITORING

1. The BoR may inspect all study activities occurring under their auspices. However, any site-inspection should be done in collaboration with the relevant partner REB and their respective institution.
2. Findings of inspections done by partner REBs at their sites should be reported to the BoR.

SITES ADDED AFTER INITIAL APPROVAL

1. Lead PI is responsible for adding sites as an amendment on PREP. The PAA must specify all required site-specific information, including site PI/QI, co-investigators, study locations, anticipated number of participants recruited, and recruitment/consent/data management procedures (as necessary).
2. Partner REB may delegate responsibility for the review to the BoR, or review the amendment as per their normal process.
3. Once provisos are satisfied, BoR issues the amendment certificate. The initial Certificate of Approval should also be manually re-issued to ensure the site PI is listed on the approval certificate with all approved study documentation (e.g., protocol, data collection forms, etc.).

STUDY SUSPENSION

1. The BoR may suspend a study in accordance with its policies without prior consultation of the partner REBs. Partner REBs must be informed of study suspension immediately.