the CTN
CIHR Canadian
HIV Trials Network

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CIHR Canadian HIV Trials Network (CTN)

Study Submission and Review Process Guidance

- General information about the CTN may be found at http://www.hivnet.ubc.ca
- Information about the CTN's structure, including details about the CTN's review committees, may be found at http://www.hivnet.ubc.ca/about/our-structure/
- The registration deadlines and submission forms may be found in the "CTN Review" section of the Research Toolbox (use Chrome as your browser if possible): http://www.hivnet.ubc.ca/research-toolbox/

After you have read this document, if you have questions, please contact:

- The CTN at 1-800-661-4664 or by email to submissions@hivnet.ubc.ca.

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Overview

The CTN Regular Study Submission process occurs twice per year and is open to CTN Investigators who have already obtained a primary source of funding for their project.

The project must be:
1) interventional;
2) approved for submission by the relevant Core Lead(s); and
3) align to the CTN's current scientific priorities (see appended Glossary of Terms).

Projects must be approved by the Core Leads for submission at the LOI stage before the CTN National Centre will invite applicants to provide a full submission. Full submissions are then reviewed by the Community Advisory Committee and Scientific Review Committee (as applicable) during the CTN's semi-annual meetings. Projects approved by these committees are then submitted to the CTN's Steering Committee who ultimately approves all CTN projects. Finally, if approved, the Funding Committee will adjudicate the project's resource needs and may allocate in-kind services (or a small amount of supplemental funds) from the CTN's National Centre to the project. CTN approved projects are subject to reporting requirements and the progress of each project is then reported annually to CIHR, the CTN's primary funder.

Project Eligibility

1) CTN Investigators who have already obtained a primary source of funding may submit to the CTN.
2) The CTN Investigator must adhere to the deadlines as published in the *CTN Submission Schedule*, for example, applicants must submit the draft Letter of Intent (LOI) form to the CTN National Centre as outlined on the Submission Schedule to begin the submission process.
3) New projects must align with the CTN's scientific priorities (see Glossary of Terms). If the project does not align with the priorities, but is innovative, the applicant must be prepared to justify, to the relevant Core Co-leads, why their respective Core should support the project.
4) To be eligible, a project must have an intervention. The following types of study proposals are encouraged:
    - Multi-centred clinical trials/research studies;
    - Cohort studies (a study assessing clinical outcomes that follows the same people over multiple time points), but only national, multi-centred observational studies that have been peer-reviewed, approved, and fully funded by another funding agency;
    - Pilot studies (a study assessing the feasibility, acceptability and/or effectiveness of an intervention or treatment) that do not fit the criteria for the CTN Pilot Study Funding Program, and if single-centred, justification must be provided;
    - Implementation science projects, preferably multi-centred and with a focus on health care innovation;
    - Community-based participatory research that aligns with the scientific priorities; and
    - Novel methodologies that advance the field will also be considered.

The following types of study proposals are <u>not eligible</u>:

- Basic science or lab-based studies that do not include any clinical research in humans;

- Development of a clinical tool or algorithm;
- Health economic analysis of projects not approved by the CTN;
- Epidemiological observation of a population with one time point;
- Disease surveillance; and
- Clinical guidelines.

Process

Engage the Cores Early in the Project Development Process

CTN Investigators and community members should endeavor to engage with the relevant Core early in the development of new research projects. The Core Co-leads can assist with joining or forming a working group that will provide consultation on project development. The Core Co-leads or working groups can also connect you to other researchers working in similar areas to help prevent competition when applying for grants. If you require an introduction to the Core Leads, please contact the CTN at 1-800-661-4664 or by email to submissions@hivnet.ubc.ca.

Engage the CTN National Centre Early in the Project Development Process

As you begin working on your grant/funding application, consider contacting the CTN National Centre for two important reasons:
1) you may require an estimate for your grant if you are planning to request CTN in-kind services (outlined in the Glossary of Terms), as it is preferable that you include these services in your grant budget request;
2) you may request a letter of support from the CTN; and
3) you can take advantage of the opportunity to improve your submission by requesting a "Pre-final" review of your project.

Pre-final Review

The CTN encourages Network investigators to contact the CTN for feedback on proposal development outside of the formal review process. Pre-final proposals may be submitted for feedback prior to submission to a granting agency or a Research Ethics Board (REB). If this type of review is requested, the CTN provides the Community Advisory Committee (CAC) and Scientific Review Committee (SRC) recommendations/input to the applicant to improve the submission only, it is not considered an approved CTN study. Investigators may contact the CTN National Centre to inquire about this service.

CTN Resource Requests

The CTN's CIHR grant funds infrastructure to support the Network, consequently, projects must have primary funding. The grant includes the cost of developing and facilitating projects and aside from the CTN Pilot Study Funding Program, it does not include the operating costs of conducting individual studies, with the exception of minor project-related expenses or site enrollment costs.

Completion of the CTN budget template is required for all applications, including those that are only requesting in-kind services, to enable a transparent review by the Funding Committee if the study is approved by the Steering Committee. In their review, the Funding Committee will evaluate the project needs and may allocate in-kind support from the CTN National Centre. Based upon the funds that the CTN currently has available, the Funding Committee may provide very limited financial funding.

A. CTN In-Kind Services

If you are planning to request in-kind services from the CTN National Centre, when completing your primary grant to fund your project, please request funds for the services to enable the National Centre to cost-recover all or a partial amount from your primary grant. In the LOI Stage, applicants must indicate which CTN services they will be requesting if invited to submit a full proposal. This assists the CTN with pre-planning for allocating resources to new studies or providing feedback to the applicant if the services are not available. A listing of the services is included in the Glossary of Terms and National Centre personnel are available to provide information about the services.

B. Fund Requests

A limited amount of supplemental funds may be requested for minor project-related expenses or site enrollment costs. In principle, the Funding Committee will only review funding requests if the funds are required to address the research question, and if the request supports the overall values, mission and vision of the CTN. Examples include funds for participant honoraria or for project community advisory meetings. Applicants requesting supplemental funds must be explicit, realistic, and provide justification for their request. Please note that a CIHR percentage cut to the approved grant IS NOT considered relevant justification for requesting funds.

The CTN Funding Committee will consider requests for the following:

- funds for participant stipends;
- funds to support the on-site activities for enrolled and active participants, for example, funds to enable the sites to complete all participant-based study procedures;
- funds for project-based community advisory committees;
- funds for elders, peer-counsellors and cultural safety training for research personnel;
- small requests to support research personnel salaries when study procedures/visits have been revised, in particular, those changes requested during the CTN review process;
- funds to support study procedure changes due to extraordinary circumstances, for example, pandemic-related changes; and
- at the Committee's discretion, additional requests may be considered.

The CTN will not provide funds for the following:

- release-time stipends or honoraria for the Nominated Principal Investigator, co-Principal Investigators or Co-Investigators with salaried academic appointments;
- direct conduct of research beyond pilot or feasibility studies;
- funds for the full operation of satellite sites for studies or adding additional sites for studies;
- “top-up” funding when a grant budget has been cut by the primary funder;
- study drugs or devices;
- laboratory supplies and testing assays;
- full salary for on-site research staff for studies, the primary grant must cover salaries;
- trainee salaries;
- equipment and computers; and
- archiving or archiving services.

If you have questions about eligible expenses, please contact the National Centre using the submissions@hivnet.ubc.ca email address.

Letter of Intent (LOI)

The Study Submission Calendar is available on the CTN website, at the following link (best if viewed on a Chrome browser): http://www.hivnet.ubc.ca/research-toolbox/. **Failure to meet the deadlines and/or the submission requirements will result in the application being rejected and the applicant will be asked to re-apply in the following competition.**

- The deadlines are provided in the Research Toolbox http://www.hivnet.ubc.ca/research-toolbox/ and the Letter of Intent (LOI) form is available at this link (in the *CTN Review Phase* section).
- The CTN Investigator must contact the relevant Core Co-lead(s) and the CTN National Centre, ideally a minimum of 30 days prior to the Letter of Intent (LOI) being due to the National Centre. The draft LOI form must be submitted to the CTN using the submissions@hivnet.ubc.ca email by the *Draft LOI to CTN* date indicated on the Submission Schedule. The CTN then provides the draft form to the relevant Core and the Core Co-leads will guide the applicant in the CTN processes, ensure the proposal aligns with the CTN scientific priorities and is methodologically sound, and then provide Core approval by signing the LOI Form prior to submitting it to the CTN on behalf of the applicant (listed as the *Core Approval of LOI* on the Submission Schedule).
- Applicants with Core-approved LOIs that meet the requirements at the LOI stage will then receive an email from the CTN National Centre to notify them that they are invited to provide a full submission. This notification email will include details about the requirements for the full submission and the deadline for the submission.
- A copy of the primary funding approval letter, the budget module, and reviews (for example, CIHR letter with reviews or a copy of the approval letter from industry) must be attached to the LOI Form. Cohort studies must be fully funded prior to submission. The CTN asks applicants to indicate which CTN services or supplemental funds they will be requesting if invited to submit a full proposal. This assists the CTN with pre-planning for allocating resources to new studies.
- The applicant must provide details about the following in the LOI form to ensure the applicant is aware that this information is required for a Full Application:
    - Any changes to the project since the primary funding application (for example, a study arm that was added after the primary review/approval);
    - Information about community consultation; and
    - Development of a recruitment plan for the project.
- When completed, the LOI Form must be emailed as an attachment to submissions@hivnet.ubc.ca.

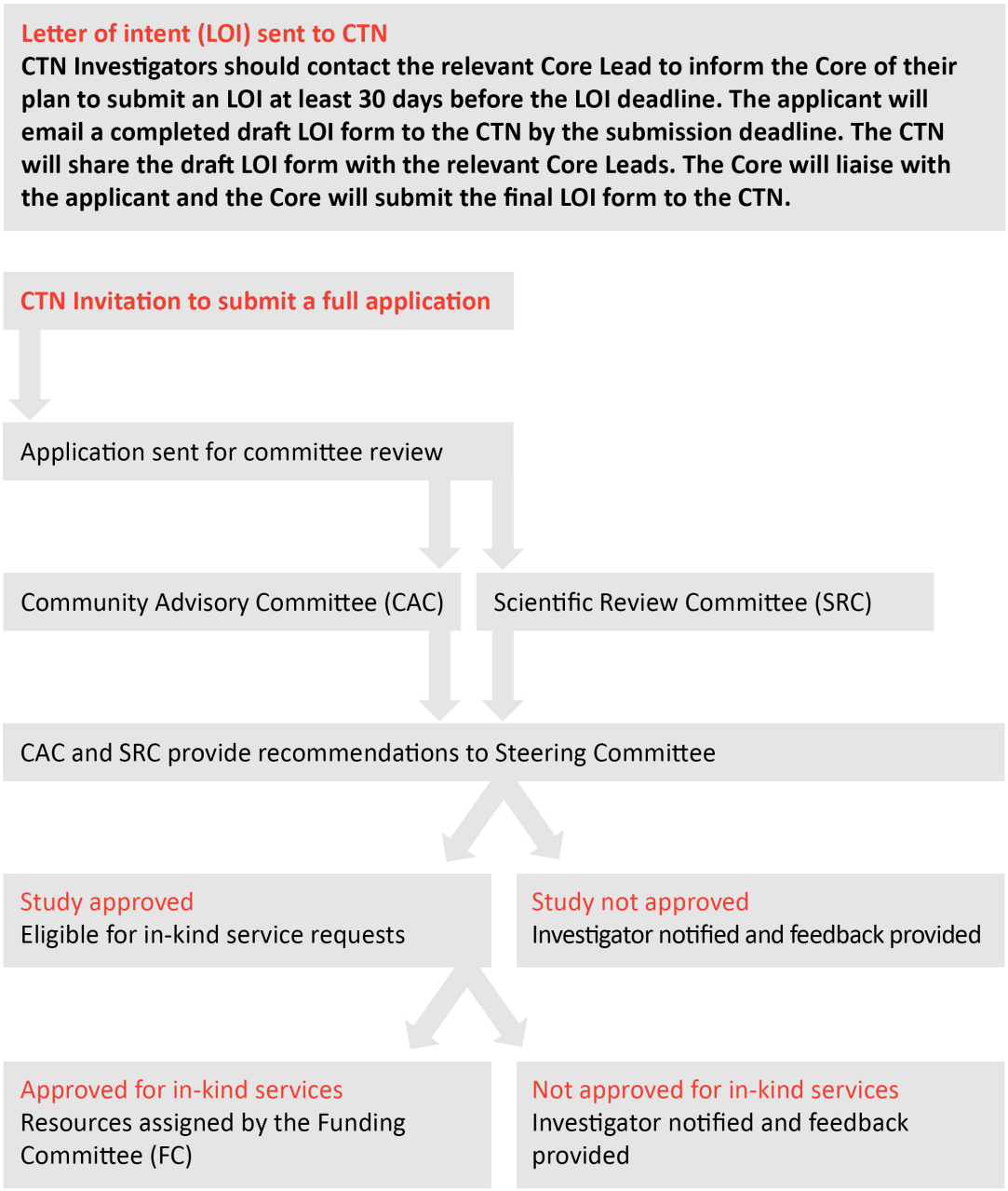
Re-submission or Additions to Current Projects

- If this is a re-submission (the applicant has already submitted this project to the CTN and it was not approved as a study), it is the applicant's responsibility to clearly demonstrate how any required changes noted by the Community Advisory Committee (CAC) and any Major Flaws indicated by the Scientific Review Committee (SRC) have been made and addressed; or
- If asking for additional funds or an arm to be added to an existing CTN study, it is the applicant's responsibility to clearly demonstrate how this request differentiates from the original submission and why it is required.

Full Application Submission

- Investigators who have been invited to submit a Full Application will be required to complete the *Full Submission Application Form*. The Form includes a Full Submission Checklist that outlines the required documents that must be submitted to support the application.
- Prior to submission, applicants must liaise with the relevant Core Co-leads to receive feedback about their submission. National Centre personnel may be contacted for additional guidance about the submission process, CTN services or general questions.
- The full submission must include the documents outlined in the Full Submission Document Requirements as listed in the *Glossary of Terms*. **Late submissions and submissions that do not include the required documents (or if not relevant to the application, justification is provided in the *Full Submission Application Form)* will not be accepted. Those forms that indicate "provided by the CTN" must be used, alternates will not be accepted.**
- When completed, the application and all attachments, saved as PDFs, must be emailed to submissions@hivnet.ubc.ca in the order listed on the *Full Submission Checklist.* Any questions may be directed to the CTN at 1-800-661-4664 or by email at submissions@hivnet.ubc.ca.
- The CTN will then provide the documents to the reviewers from each of the required review panels. The reviewers are encouraged to submit questions for the applicants back to the CTN. The CTN will provide the list of questions to the applicants and applicants are required to respond to the primary reviewer questions within the timeframe outlined by the CTN (approximately one week).

Figure 1: CTN Full Submission Review and Approval Process



CTN Review Process

While Figure 1 provides a visual representation of the process, please review this section for a full description of the review process. The documents submitted to the CTN are assigned CAC and SRC (if applicable) reviewers. If the reviewers have questions for the applicant, the CTN will provide the questions to the applicant with a due date for a response (approximately one week). The submission documents, including responses to primary reviewer questions, are provided to the CAC and SRC (if applicable) for further discussion during their meetings. Should the project meet the community perspective criteria, as well as the scientific review and methodology criteria for CTN projects, it is brought to the Steering Committee (SC) for a final discussion and review. The Funding Committee (FC) determines the level of support (services or small supplemental funds) that the CTN can provide to the project.

All committee members are bound by confidentiality agreements. Information about the review committees may be found at: http://www.hivnet.ubc.ca/about/our-structure/committees/

CAC Review

The CAC reviews all submissions and may ask for required/recommended changes to the informed consent form(s) and pose questions to the investigator regarding the informed consent form. When projects are approved by the CTN, the investigator must respond to CAC and receive notification that CAC is satisfied with the responses before the CTN can proceed with the approved services or release funds. If a project is not approved, but the investigator plans to re-submit to the CTN, the investigator must address the CAC required/recommended changes in their resubmission.

SRC Review

All submissions will undergo SRC review unless the project is approved by a recognized peer-review panel (for example, CIHR's Project Grant review panels or select NIH review panels). If the project submitted is the exact project reviewed and approved by the peer-review panel, in such cases, a review by the SRC is not necessary, however, all reviews must be included in the submission. If the investigator has made any changes to the project since the primary review by a recognized peer-review panel, the project must undergo SRC review. Successful applicants are required to respond to any SRC required/recommended changes, in writing.

Projects that are not approved may be re-submitted, in the next review cycle, but must include any new information *and* the changes suggested by the review panels.

SC Review

Submissions approved by the SRC (if applicable) and CAC (including recommended or required changes) are presented to the Steering Committee (SC). The SC then reviews the submissions and makes the final decision to approve the submission. Once approved, a CTN number is assigned to the project.

Funding Committee Review

All SC-approved projects are reviewed by the Funding Committee (FC) for resource allocation. There is no guarantee that the Funding Committee will approve the CTN services or supplemental funds requested by the applicant. Upon review, the FC may determine that the CTN should cost-recover all or partial funds from grants that have already received funds for services (for example, statistics and data management). It is possible that CTN-approved projects will receive no additional resource support. The applicant must complete the CTN Budget template and provide all relevant financial details to ensure that the FC has the opportunity to complete a thorough review.

Post-Approval Process

Within eight weeks of the reviews, the applicant will receive correspondence from the National Director that outlines the results of the reviews and describes the resource allocation. Successful applicants are required to respond to CAC and SRC required/recommended changes, in writing. The SC and FC may also request additional details from applicants. **CTN in-kind services and supplementary funds will not be allocated to the project until the applicant(s) have provided their written responses to the Review Committees, and the committees are satisfied with the responses.**

Investigators of CTN-approved projects are required to provide the CTN with reports, quarterly enrolment updates, documents, and are required to acknowledge CTN support when issuing publications, scientific presentations, press releases, and other documents describing projects or programs supported by the CTN in whole or in part. The CTN Publication Guidelines are available online and are provided to successful applicants. Investigators who suspend CTN-approved projects, for any reason, are required to report this suspension to the CTN immediately.

The CTN cannot grant final approval to a submission until all of the required information has been received. In the case of a re-submission, all required changes and/or revisions must be included with the resubmitted documents.

To undertake their project, successful applicants are required to complete the necessary requirements for their home institution, these include:

- Fulfilling their institutional Research Ethics Board requirements.
- Participating, as required, in the progress of contract negotiation between their home institution and the CTN National Centre and responding to their home institution in a prompt manner to ensure that contract negotiations occur in a timely fashion.
- Establishing a grant account per the requirements of their home institution, oversee (if applicable) spending for the study, and provide the CTN National Centre with financial statements as required.

Glossary of Terms

Email submissions@hivnet.ubc.ca if you have questions or require clarification.

CTN Cores – The CTN has four scientific Cores. This structure was designed to support our Investigators and community members— emerging and experienced — to generate new concepts and protocols. The Cores strive to ensure that implemented studies remain focused on key scientific priorities while also providing flexibility to address new scientific innovations as they emerge. The Core structure is equipped to provide a forum for dynamic discussion of research ideas and the rapid movement of research initiatives into clinical trials and studies.

The four Cores are:

1) Clinical Care & Management (CCM)
2) Co-Infection & Related Conditions (CRC)
3) Prevention (PREV)
4) Vaccines & Immunotherapies (VIT)

Each Core is led by two Co-leads.

CTN Investigators – Only CTN Investigators may apply to the CTN. To become a CTN Investigator, an applicant must be qualified (as outlined in the CTN New Investigator Application Form) and agree to the terms outlined on the CTN Investigator Affiliation Agreement. See the *Become a CTN Investigator or Postdoctoral Fellow* section of the CTN Research Toolbox: http://www.hivnet.ubc.ca/research-toolbox/

CTN Review Committees:

Community Advisory Committee (CAC) – The CAC is a broadly representative group of people from across Canada who are living with HIV and/or representing organizations fighting the epidemic. This committee reviews all protocols and informed consent forms submitted to the Network and makes recommendations to the Steering Committee (SC). It also advises the Scientific Review Committee and CTN Investigators and informs the SC about the research priorities and concerns of Canadians living with HIV or other Sexually Transmitted Blood Bourne Illnesses (STBBIs).

Scientific Review Committee (SRC) – Scientists, physicians, and members of the HIV community are represented on this committee, which makes recommendations to the Steering Committee (SC). Members meet twice yearly and up to four times by teleconference to provide peer-reviews of proposals submitted to the CTN. They evaluate the scientific merit of experimental therapies, as well as the design of trial protocols to ensure that all CTN trials are relevant and based on validated methodology.

Steering Committee (SC) – This expert group of scientists, people living with HIV, and other stakeholders serves as the CTN's Board of Directors. Drawing on its broad range of expertise and knowledge of national and international trends, members consider the recommendations of other Network committees and may set research priorities.

Funding Committee (FC) – The FC determines the CTN's resource allocation to CTN approved projects. These resources may be in-kind or limited financial funding. All projects must already have a primary source of funds before they are submitted for CTN review and approval.

Data Safety and Monitoring Committee (DSMC) – Experts in HIV clinical care, research design, biostatistics, and law are among the members of the DSMC. The DSMC meets twice per year to monitor the safety and efficacy of CTN-approved interventional studies in progress, in particular, clinical trials. Applicants may request this service if their study does not have its own DSMC. The committee will also occasionally review preliminary analyses of study results or new information and recommend changes in protocol, procedures, or the termination of a study.

CTN Scientific Priorities

Principles that are included in all themes:

- Focus areas are HIV and STBBIs;
- Key populations include:
    i. Indigenous Peoples
    ii. Men who have sex with men (MSM)
    iii. People from HIV/STBBI-endemic countries
    iv. People with mental health challenges
    v. People who use (inject) drugs (PWUD)
- Community engagement as the CTN wishes to continue to provide an inclusive, positive, and collaborative environment for all communities; and
- Partnering with key population advocacy and service organizations.

1) Prevention

a. Developing and testing interventions for prevention and harm reduction (for example, PrEP).
b. Developing and testing strategies for early detection and treatment of HIV, HCV, HPV, syphilis, and other STBBIs.

2) Optimizing Health Outcomes

a. A focus on treatment strategies and improving health outcomes for persons living and aging with HIV and STBBIs. This includes:
    i. Developing interventions to decrease the risk of comorbidity and death while improving health outcomes and decreasing health disparities.
    ii. Assessment of the role of inflammation, major organ dysfunction, antiretroviral agents, genetics, the microbiome, viral co-infection, alcohol, drug use, and/or lifestyle factors on the risk of co-morbidity and cancer.

3) Cure

a. Collaborating with basic sciences to study innovative approaches to seek cures for HIV: this may include, but is not limited to, strategies to impact immune activation and depletion of viral reservoirs.

However, innovative research that advances the field will also be considered.

Full Submission Document Requirements

Applications submitted late or without the required documents will not be accepted for review. As outlined in the *Full Submission Checklist* located on the first page of the *CTN Full Submission Form,* submissions must include the following, in the order listed below. If the following are not included, the applicant must provide justification why in the relevant section of the *CTN Full Submission Form.*

- Completed *CTN Application Form* (provided by the CTN)
- Completed *CTN Study Proposal Form* (provided by the CTN)
- The participant Informed Consent Form
- Completed *CTN Recruitment Plan* (provided by the CTN)
- Community Engagement Plan
- Completed *CTN Budget Template* (provided by the CTN)
- A copy of the primary grant/funder (including the budget and budget justification, and all appendices) application, a copy of the approval letter and all reviewer comments. You must include the budget provided to grant/funder.

Supporting documents (only include if applicable):

- If a clinical trial, the Health Canada "No Objection Letter" (if received) and information about drug/device procurement from the vendor/manufacturer (e.g., a letter from a pharmaceutical company guaranteeing provision of a study drug, placebo, and investigational labelling for the trial and/or a letter from the drug manufacturer that outlines the purchase price of the study drug, placebo, and investigational labelling for the trial).
- Any other documentation available that may be relevant for the review of your project. Examples could include documents such as case report forms, investigator's brochures or product monographs, and letters of support from community groups or community advisory boards.

In-Kind Services – The CTN National Centre in-kind services available for request:

- Protocol Development: incorporates many of the services listed below.
- Data Management services may include: case report form generation, database management, data management system creation, and data queries.
    - Consultation for the development of case report forms and database set up during start up only, the investigator or their study team is expected to enter, manage, and clean their own data.
- Statistical and Methodological consultation may include: developing study methodology (e.g., quantifying research objectives, sample size calculation, statistical analysis plan), data analysis, interpretation of results, and reviewing draft manuscripts. In addition, this group can provide consultation on automated randomization systems for studies.
- Health Economics analysis (may only be requested for CTN-approved studies, either previously approved or for the current application): design of health economics studies; conducting economic evaluations of various health interventions; performing systematic reviews and meta-analysis commonly required in cost-effectiveness decision analytic modeling; and evaluating health policies, such as drug pricing regulations. Our health economists have also developed instruments to measure and value the impact of health on patients' work productivity, which

enables employers and payers to understand the broader economic impact of health interventions.

- Regulatory Affairs services may include: protocol review to ensure that protocols are regulatory compliant; completion and submission of Clinical Trial Applications (CTA and CTA-A which are amendments to the original submission) to Health Canada and other jurisdictions; pharmacovigilance and Serious Adverse Event (SAE) reporting per regulatory agency requirements; and the CTN, on behalf of the lead investigator, may become the primary contact for ongoing regulatory correspondence with the study sites (for completion of Qualified Investigator Undertakings and REB Attestations) and Health Canada (Clinical Trial Site Information Forms and SAE reporting).
- Monitoring services (for Health Canada regulated clinical trials) may include: trained and certified monitoring staff who develop risk-based monitoring plans and who may conduct on site and/or remote monitoring to assess data quality, regulatory, and protocol compliance. In addition, we can provide support for regulatory inspections.
- Project Management services (may only be requested for multi-centre studies): assistance completing protocol and informed consents; recruitment plan; budget development; study operations manuals; study management of multi-centre studies; training study staff on protocol requirements (site procedures and investigator's meetings); liaising with vendors on investigational product and laboratory requirements; and ensuring quality and accountability procedures, as required by regulatory agencies, are provided for each study.
- Data Safety and Monitoring Committee (DSMC): interventional studies require unbiased review of the safety and efficacy of new interventions or studies in progress to ensure that the safety of participants is protected. The CTN's DSMC meets two times per year and provides information about the safety and efficacy status to the lead study investigator.
- Communications and Knowledge Translation: All CTN studies receive bilingual plain language study descriptions to promote their studies on the CTN website and on CATIE's website, listing in Connections newsletter, promotion through social media channels, and community outreach through articles and presentations. Additional services, on request, may include: social media campaigns for studies, production of study documents and materials; assistance with press releases and interactions with the media; integrated and end-of-grant knowledge translation plans; and support for the development of policy documents.
- Other services may include: assistance liaising with other external parties to gain extra resources for studies; program evaluation; and training related to CTN projects.

Types of Submissions – There are three types of submissions:

- Pre-final Proposal – Network Investigators may contact the CTN for feedback on proposal development outside of this formal review process. Pre-final proposals can be submitted for feedback prior to submission to a granting agency or a Research Ethics Board (REB). In this case, the CTN provides Community Advisory Committee (CAC) and Scientific Review Committee (SRC) recommendations/input for pre-final applications to improve the submission for funding application.
- Final Proposal – These are new submissions that were approved, after LOI registration for submission for a full review by the CTN.

- Re-submissions – These are submissions that were previously reviewed and not approved by the CTN. Unless expressly instructed, CTN Investigators must re-register their re-submission during the LOI phase of review.