Building the Future of Clinical Trials at the Canadian Institutes of Health Research

Response from C4T

November 23, 2022

THE CANADIAN COLLABORATIVE FOR CHILDHOOD CANNABINOID THERAPEUTICS

Overview

The Canadian Collaborative for Childhood Cannabinoid Therapeutics (C4T) is a multidisciplinary team made up of clinicians, scientists, decision makers, parents and youth partners with interest and experience conducting high-quality research on cannabis used for medical purposes. As a research team who designs and implements innovative patient-informed clinical trials, we have provided responses to specific questions outlined in this consultation to facilitate the development of a sustainable and inclusive long-term clinical trials strategy for CIHR. C4T currently holds funding from CIHR and other funders to design and conduct clinical trials in Canada.

This response was prepared and submitted by Sophia Mbabaali MA, and Lauren Kelly, PhD Scientific Director, C4T on November 23, 2022.

Conflicts of Interest Statement: Dr. Kelly was a Scientific Advisory Board Member for the Health Products Containing Cannabis Committee at Health Canada (2020-2022) and currently sits of on the Board of Directors for the Canadian Consortium for the Investigation of Cannabinoids (CCIC). Dr. Kelly holds academic funding from the Canadian Institutes of Health Research, SickKids Foundation, Canadian Cancer Society, Mitacs, Children's Hospital Research Institute of Manitoba and Research Manitoba.

Our members list and ongoing research collaborations can be found on our website: **www.medcannkids.ca**

CIHR Funding for Clinical Trials

Are there gaps in CIHR's funding programs which create barriers to implementing clinical trials for researchers?

Across Canada **institutions are not equally supported** to develop innovative clinical trials (iCT) with smaller academic centres lacking regulatory/scientific support to initiate clinical trials in efficient timelines, let alone be successful in clinical trial funding competitions. A lack of institutional commitment to expedite CIHR funded clinical trials can result in recruitment delays, hinder investment from industry and increase timelines before the first patient can participate in these trials.

Developing strong, diverse teams to design and conduct clinical trials requires time and investment. A 3 year timeline along with an extremely short application period hinders investigators who do not already have an established research network or program, have caregiving responsibilities, and/or are required to take medical leaves. This lack of sustained funding beyond 3 years requires investigators to repeatedly build capacity to conduct iCTs once funding is granted, and the current system for developing investigator-initiated trials is a barrier for researchers.

Permanent infrastructure to support a **pan-Canadian learning healthcare system** similar to the model implemented in the National Health Services (NHS) in the United Kingdom is warranted to sustain iCTs over the long term in Canada. This will require a federal mandate with collaboration from all provincial and territorial health authorities, not just an investment of funding.

Beyond conflict-of-interest considerations, what guidance is needed for stakeholders and partners to support successful partnerships under CIHR funding programs?

There is a need for CIHR to develop policies that hold research teams **accountable for engaging in responsible research practices**, as well as developing and maintaining meaningful relationships with patient partners. Moreover, accountability policies for institutions to transparently report how indirect funds are being used to support investigators' clinical trials are also needed. In developing this **policy for institutional use of indirect funds for clinical trials**, CIHR should outline best practices for use of these funds by institutions in supporting clinical trials using real world examples.

Internally, CIHR needs to be held **accountable for shortcomings** observed in past funding competitions, including but not limited to inadequate time between the launch of funding competitions, changing application deadlines, frequent changes to eligibility criteria and delays to the anticipated notice of decision date. These shortcomings have curated a sense of mistrust toward CIHR from research teams and their patient partners. A public statement from CIHR assuring future competitions will adequately consider the time and effort it takes to build trials partnerships.

Last of all, if future clinical trial fund applications are to be adjourned by an independent body such as BLSS (non-standard peer review committee) these should be **reviewed for competition fit at the registration phase**. Allowing research teams who are not aligned with directed funding to submit applications fuels mistrust, wastes valuable resources and contributes to research waste and burnout.

Innovative Clinical Trials

How can CIHR further support the development of innovative clinical trials?

A top-down education approach (which requires institutional support and partnership with CIHR), peer-reviewers and research ethics boards will encourage fair review and support the development of iCTs. Specific competitions with clear criteria for innovation will be required to support the development of these innovative trials. These competitions should further serve as examples highlighted by CIHR to encourage funding of iCTs in all competitions. **Past CIHR competitions about innovative clinical trials should be showcased** (e.g., number of trials funded, results/impact) to demonstrate their feasibility to the scientific community and the general public. CIHR should also reflect on the strengths and limitations of these past competitions and apply the lessons learned when launching future competitions for iCTs. While there remains justification for utilizing traditional methods, maintenance of the status quo will not support the desired development of iCTs in Canada.

An in-depth analysis of all clinical trials funded by CIHR is required to identify gaps and strengths in the Canadian landscape. This can then fuel discussions about what developments are required to support iCTs. Once iCTs are funded, CIHR should take measures to highlight these innovative trials to the general public to demonstrate their feasibility and their potential impact on the health and well-being of Canadians. Measures to ensure award holders have implemented and acted on their proposed knowledge translation strategies should also be enacted by CIHR during that time.

Are there new areas of innovation in clinical trials that should be included in iCT initiatives?

CIHR should develop a **priority funding mechanism for trial innovations in all open competitions** such as:

- Application of adaptive and/or platform designs
- Dose finding and pragmatic designs
- Prospective meta-analysis'
- Virtual models (remote trials)
- Integrated mixed-methods
- Incorporation of health technology assessment (health economics)

Clinical Trials within Canada's Biomanufacturing and Life Sciences Strategy

Are there areas where increased clinical trials support could help build Canada's biomanufacturing and life sciences sector?

Institutions across Canada are **not equally prepared or interested in supporting biomanufacturing or clinical trials**. This creates inequities in both the innovations tested and research teams funded. In consultation with Canadian institutions, CIHR should explore how these inequities ultimately influence funding decisions and what actionable changes can be made to support institutions with less infrastructure and resources. Furthermore, it is unclear what the review process for the Biomanufacturing and Life Sciences Strategy (BLSS) entails and what encompasses their criteria for supporting clinical trials. Transparency from CIHR around the processes used by the BLSS is need to bridge these gaps.

Are there additional funding streams that would also be useful for continuing to build the domestic biomanufacturing and life sciences sector and Canadian clinical trials ecosystem?

In recognizing the value and importance of patient engagement throughout the lifecycle of a clinical trial, CIHR must acknowledge that **building relationships with people with lived and living experience (PWLLE) and communities takes time, expertise and adequate resources.** Moreover, some investigators and research teams may be novices at conducting patient-oriented research and will require additional support to engage in this practice. An increase in planning and dissemination grants within each institute to support investigators developing partnerships with PWLLE will provide the necessary funding for research teams to begin or continue this work prior to submitting grant applications to fund these clinical trials. CIHR should establish an **open pool with simple deliverables** for any research team to annually fund patient engagement – these small amounts of funding (approx. $5,000) go a long way to bringing more patient voices to the table in trials and ensuring best engagement practices (e.g., compensation) for patient partners. Calls for Canadian Teams to participate in i**nternational clinical trials** should run annually as these are extremely important for providing generalizable data for regulators. Funding for **SWATS (studies within trials) and methods development** are critical to ensuring evidence based trials.

With respect to training programs, how can investigators be best supported to lead well-designed and impactful clinical trials?

Building a research team with the expertise and capacity to develop and implement impactful clinical trials requires **protected time for clinicians**, and **investment in trainees**.

To support investigators in the aforementioned areas, CIHR should:

- Allow grant funds to be used to provide compensation for clinicians and other health care professions who often lack **protected research time**
- Require **higher stipends** (annually adjusted for inflation) be paid to trainees to facilitate retention and their interest in science

The Canadian Clinical Trials Ecosystem

What barriers do researchers encounter when navigating the different steps (e.g., funding, contracts, ethics approvals) and organizations in the Canadian clinical trials ecosystem?

Establishing **contracts** between institutions across multiple provinces is a lengthy and tedious process, which often results in significant delays to research timelines and participant enrollment. CIHR should encourage the development of standing contracts within institutions across provinces that can easily be modified for specific study protocols.

Researchers also encounter many challenges when working to acquire research ethics approval across institutions. A sustainable clinical trials strategy should include a centralized process for research ethics to mitigate these barriers. In addition to the Canadian Collaboration for Child Health: Efficiency and Excellence in the Ethics Review of Research (CHEER), significant efforts should be made to develop a **pan-Canadian ethics harmonization** for the adult population to streamline the research ethics review for multi-site clinical trials.

Locating competitions with small pots of funding available for research teams to generate multi-site pilot data, develop innovative methods, and conduct patient engagement has also proven to be difficult. Increasing the number of **planning and piloting grants specific to clinical trials** within each institute would provide research teams with the necessary funding to begin or continue this important work prior to submitting grant applications to fund clinical trials.

What enabling activities or policies should CIHR establish for funded clinical trials research that would support streamlining and efficiencies in the Canadian clinical trials ecosystem?

CIHR needs to implement policies surrounding institutional use of indirect funds and provide guidance documents to these institutions outlining **best practices for use of indirect funds that supports the needs of investigator-initiated trials**. The lack of transparency around the use of these funds by institutions and lack of accountability for institutions who neglect to provide operational support to investigators warrants investigation by CIHR.

Are there practices used by other organizations that CIHR should learn from and/or form partnerships within the development of a national clinical trials strategy?

The current iteration of the **Canadian Common CV** used by CIHR has caused barriers for international collaborators and non-academic partners. The minute level of information requested has proven to be burdensome for the majority, especially individuals who do not regularly interact with Canadian research systems. CIHR should consider **adopting a simple and straight forward tool such as Biosketch** used by the National Institutes of Health that is able to capture individuals' experience and expertise without imposing a significant burden on applicants.

CIHR should also take steps to create **an open repository for reports** from all funded research. Alongside this development, CIHR should amend annual and final reporting requirements to include additional study details. In alignment with recent reporting requirements from the New England Journal of Medicine, investigators should be required to submit a supplementary table outlining the representativeness of study participants (i.e., sex and gender, age, race or ethnicity etc.) in their final report. This would provide researchers an opportunity to highlight the representativeness of the study population and generalizability of the study findings. Compiling this information in a central and accessible space will foster transparency and trust between CIHR and the general public.

Lastly, to enhance the landscape long-term in Canada, investment from corporate partners will be needed. CIHR should explore the feasibility of putting forth **funding calls for clinical trials in partnership industry.** Exploring these unique investment opportunities will help expand CIHR's current list of partnerships and stakeholders, while also creating opportunities for investigators to conduct clinical trials in specific research areas (e.g., pediatrics, rare diseases, maternal, fetal and neonatal health).

What policies should CIHR consider with respect to ongoing monitoring of the status and performance of trials in order to maximize the value and impact of clinical trial research?

As a condition of receiving indirect funds, CIHR should require institutions to submit an annual report outlining all ongoing trials at their institution. Due to the current lack of transparency, reports highlighting the current status of these trials along with their value and impact for Canadians should be developed for the information of CIHR and the general public, respectively.

CIHR Policies to Support Equity, Diversity and Inclusion (EDI), Transparency, and Research Excellence

Are there additional specific policies or design elements in funding opportunities that CIHR can use to further support equity, diversity and inclusion in clinical trials, including addressing barriers to clinical trial participation?

Submitting a competitive grant application to CIHR requires significant time, expertise, consultations, and resources from the Nominated Principal Applicant (NPA) and larger research team. Inadequate time between the launch of funding competitions and application deadlines ill prepares investigators to submit a high-quality application. CIHR should always provide ample time (3 months+) for research teams to generate a strong grant application, absent of time constraints imposed by CIHR without cause.

To further foster equity, diversity and inclusion, CIHR should require all funding applications include a statement outlining what is known about the current barriers to participation among the study's target population with action items outlining how these barriers would be mitigated in the proposed clinical trial. CIHR should also create measures to **ensure a portion of funding awards are granted to investigators conducting clinical trials targeting underrepresented groups in health research (e.g., pediatrics, rare diseases, maternal, fetal and neonatal health)**.

Finally, CIHR should **directly request feedback** from applicants involved in the most recent Clinical Trials Fund and those who have submitted Randomized Clinical Trials to the Project Grant competition to identify how shortcomings in these competitions resulted in **inequities among investigators**/teams funded. An exploration into the barriers investigators faced in relation to intersectionality will be fruitful for CIHR's understanding of these challenges, and provide an opportunity to mitigate these barriers in future competitions.

Development of a Long-Term Clinical Trials Strategy

Looking to the future, what key elements – in addition to funding – should a sustainable Canadian clinical trials strategy include?

Coordination amongst provinces to remove legislative barriers that hinder multi-provincial clinical trial harmonization efforts such as privacy legislations and data sharing is a pivotal and key element to developing a sustainable strategy for clinical trials in Canada.Trust with the public and investment from industry are also critical to a sustainable research environment, and will be key to increasing Canada's share in global clinical trials landscape. To do this, open discussions with investors (industry, non-governmental organizations (NGOs), etc.) as to limitations and potential regulatory incentives for investing in clinical trials in Canada is needed.

Additionally, an **open repository of all CIHR funded clinical trials, their results and impact could increase trust and investment from the general public, industry and NGOs.**

Finally, CIHR should conduct an exploration into how to increase clinical trial capacity for investigators located at smaller institutions and hospitals who often lack the capacity to participate in clinical trials, but have an interest in being involved. A lack of operational resources and permanent staff hinders the ability for investigators at these sites to develop and implement innovative clinical trials. To minimize these challenges, CIHR should consider establishing a **central repository for operational support that can be outsourced** to smaller institutions and non-academic centres who require additional support for running clinical trials. Having ongoing exploratory discussions with these smaller research institutes can help CIHR identify what supports are needed to expand targeted funding efforts to increase clinical trial participation for Canadians residing outside of non-academic centres.

Any questions or requests for clarification can be sent to **lauren.kelly@umanitoba.ca.**