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Innovative approaches to investigator-initiated, multicentre paediatric clinical trials in Canada

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BMJ Open Innovative approaches to investigator-initiated, multicentre paediatric clinical trials in Canada

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ABSTRACT

Data from clinical trials are needed to guide the safe and effective use of medicines in children. Clinical trials are challenging to design and implement in all populations, and children present additional considerations. Several regions including the UK, USA and Europe have established clinical trial infrastructure to capitalise on expertise and promote clinical trials enrolling children. Our objective is to describe the partnerships and operational considerations for the development of paediatric clinical trials infrastructure in Canada. We describe the design and conduct of four emergency room paediatric trials, with four separate sponsors, across four provinces in parallel. Operations discussed include multisite contract development, centralised risk-based data monitoring, ethical review and patient engagement. We conclude with lessons learnt, additional challenges and potential solutions to facilitate drug development for children in Canada.

INTRODUCTION

Due to the historical exclusion of children from clinical drug trials, paediatric health-care providers have only minimal safety and effectiveness data to guide their daily prescribing practices. More than 50% of children in Canada require at least one prescription medication each year.¹ Off-label drug use (ie, without regulatory authorisation based on direct empirical evidence from clinical trials) is commonplace and may lead to over- or under-dosing of children, carrying the inherent risks of adverse drug reactions and suboptimal clinical effectiveness. Critical issues influencing the development and evaluation of medicines for children in Canada were summarised as the following key findings, quoted from an expert panel report released by the Council of Canadian Academies in 2014:²

i. Children take medications, many of which have not been proven safe and effective for their use;

- ii. Children respond to medications differently from adults; thus, medications must be studied in children and formulated for children;
- iii. Studying medicines in children is always possible and in their best interests;
- iv. In the USA and Europe, paediatric medicines research is encouraged, required and monitored in ways that offer lessons for Canada; and
- v. Paediatric medicines research is a Canadian strength, but it requires reinforcement and sustained capacity and infrastructure to realise its full potential.

Several economical, ethical and logistical challenges specific to conducting clinical trials for children have contributed to gaps in the current evidence base for the use of medicines in children.^{1,3} Given that most of the drugs in question have already been developed and licensed for use in adults, there is a notable lack of industry incentive to organise or fund trials in children. This places the financial burden of very expensive research squarely on government and not-for-profit agencies, academic institutions and clinical investigators, who have access to comparably less, and highly competitive, funding. Compounding this is the relative infrequency of many serious childhood illnesses, making it difficult to answer most research questions through enrolling participants at a single centre. To recruit a sufficient number of participants in a timely fashion, paediatric clinical trials usually involve multiple sites, resulting in considerable complexity in negotiating larger budgets, establishing contracts and data sharing agreements and carrying out multiple institutional ethics reviews.⁴

In April 2016, the Canadian Institutes of Health Research launched the 'Strategy for Patient-Oriented Research innovative



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Clinical Trials Initiative' to increase Canada's competitiveness in clinical trial research, stimulate adoption of novel trial methodologies and build capacity for innovative clinical trials (see Related Links for more information). Recognising the need for national infrastructure to address the challenges listed above, as well as the need to improve trial design to adequately inform decision-making, a team of Canadian paediatric investigators was successful in securing funds for a multi-year project entitled 'Innovation in Paediatric Clinical Trials (iPCT)'. The binary aim of the iPCT project is to demonstrate that both methodological innovation and efficiencies through centralised data management and trial coordination will allow the generation of evidence that will have an immediate impact on paediatric clinical decision-making.

The iPCT project is the initiative of a nascent, national paediatric clinical trial network known as KidsCAN Trials (see Related Links for more information). In seeking to build, test and establish national infrastructure to conduct paediatric clinical trials in Canada, the KidsCAN Trials steering committee engaged a well-established national research network in paediatric emergency medicine, Paediatric Emergency Research Canada (PERC) for collaboration.⁵ Four specific clinical trials, led by four experienced clinician-scientists in paediatric emergency medicine, were chosen to create an environment in which several innovative approaches to conducting paediatric clinical trials could be tested. These four trials themselves have intrinsic research value for paediatric emergency medicine and reflect conditions or procedures commonly encountered in the paediatric emergency department: bronchiolitis, musculoskeletal injuries, procedural sedation and acute gastroenteritis. Beyond the empirical results of each trial, however, lies the synergistic value of conducting four multicentre clinical trials in parallel. There are financial challenges for investigators to engage a Contract Research Organization (CRO) and there are limited options with paediatric expertise in

Canada. The intended outcome of the iPCT project is to finish these trials with established infrastructure that will not only have assisted the PERC network and built new knowledge in paediatric emergency medicine, but will also endure and expand, at least as proof of principle, to allow KidsCAN Trials to support drug trials in all areas of paediatric medicine. This article aims to summarise the innovative approaches taken in trial management and data coordination to maximise the return on investment in these four investigator-led clinical trials conducted in parallel across six Canadian paediatric health centres. While centralised statistical and decision-making analyses are also part of the project goals described above, the outcomes of the iPCT project in this regard have yet to be finalised and as such will be presented in a subsequent article when available. Here, we describe the key partnerships and the centralised structures and activities that form the foundation for this initiative: centralised management, centralised risk-based safety monitoring, ethical review and patient engagement. We follow with a discussion of challenges and solutions and conclude with our key messages.

Partnerships

The iPCT project emerged from, and is supported by, extensive partnerships among existing organisations. This has allowed us to capitalise on existing local paediatric clinical research infrastructure in Canada, to facilitate launching of this project (see figure 1 and Related Links for more information).

KidsCAN trials

KidsCAN Trials was established in 2016 and is a national hub to coordinate research, training and knowledge transfer in the safe therapeutic use of medicines for children. By bringing together academic child health centres and their affiliated research institutes, KidsCAN Trials encourages the uptake of new clinical trial methods and

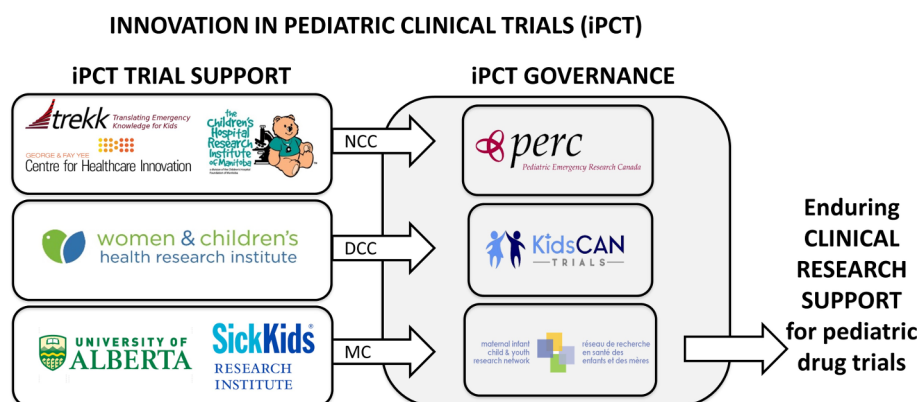


Figure 1 Partner organisations in the formation and operation of the iPCT project network. Partnerships comprise academic, not-for-profit and government organisations across provincial jurisdictions. The role of each organisation listed is described in the text. CHI, George and Fay Yee Centre for Healthcare Innovation; CHRIM, Children's Hospital Research Institute of Manitoba; DCC, data coordinating centre; iPCT, Innovation in Paediatric Clinical Trials; MC, methods core; MICYRN, Maternal, Infant, Child and Youth Research Network; NCC, network coordinating centre; PERC, Paediatric Emergency Research Network Canada; TREKK, Translating Emergency Knowledge for Kids; WCHRI, Women and Children's Health Research Institute.

knowledge transfer tools for developing and testing medicines for children.

Paediatric emergency research Canada

PERC was established in 1995 with the aim of conducting research to improve outcomes in children brought to the emergency department for acute care.⁶ At the time of writing, PERC has 21 ongoing studies, 11 of which are clinical trials, and has received more than \$39 million in research grant funding. PERC's membership includes physicians, nurses, research managers, coordinators and postgraduate trainees from across Canada.

Translating emergency knowledge for kids

Translating Emergency Knowledge for Kids (TREKK) is a Canadian knowledge mobilisation network focused on developing and disseminating evidence-based tools and resources for caregivers and clinicians. TREKK's parent advisory group has been central to the iPCT project in providing feedback on study design and the development of the assent form described under 'Ethical Review' below. TREKK's central administration is located in Winnipeg.

Maternal infant child youth research network

Maternal, Infant, Child and Youth Research Network (MICYRN) is a federal not-for-profit, charitable organisation founded in 2006 to build capacity for high-quality applied health research. It links 20 maternal and child health research organisations across Canada and provides support to new and emerging teams. MICYRN and KidsCAN Trials are leading the research ethics board harmonisation initiatives and fostering national collaboration among patients, families, child healthcare institutions, researchers, educators and regulators.

Children's hospital research institute of Manitoba

Children's Hospital Research Institute of Manitoba (CHRIM) is supported by the Children's Hospital Foundation of Manitoba and collaborates with partner organisations to facilitate innovative research activities focused on improving the health of children. CHRIM hosts the Network Coordinating Centre for the iPCT project, in Winnipeg.

George and Fay Yee centre for healthcare innovation

George and Fay Yee Centre for Healthcare Innovation (CHI) is a partnership between the University of Manitoba and the Winnipeg Regional Health Authority. It provides seven platforms which offer research expertise and services to facilitate development and implementation of evidence-based patient engagement initiatives. As part of the iPCT project, the CHI is providing training and consultation in patient engagement. In addition, it will lead the development of an online portal to share templates as well as training and educational resources for paediatric clinical trials.

Women and children's health research institute

Women and Children's Health Research Institute (WCHRI), located in Edmonton, Alberta, is supported by the Stollery Children's Hospital and the Royal Alexandra Hospital Foundation in partnership with the University of Alberta and Alberta Health Services to improve the lives of women and children through research. The Data Coordinating Centre, located at WCHRI, supports the data management needs of this and other child health research networks. The Quality Management in Clinical Research department at the University of Alberta serves to meet the regulatory requirements of the university in the conduct of clinical trials through quality management and trial monitoring.

The hospital for sick children (SickKids) research institute

Located in Toronto, this research institute is supported by the SickKids Foundation and collaborates with partner organisations to facilitate innovative research activities focused on improving the health of children. Clinical trial methodologists based here, within the Child Health Evaluative Sciences Programme lead the Methods Core for the iPCT project, as described below.

Centralised management

Our iPCT network consists of several trial-specific nodes of coordination operating in partnership with a central network coordinating centre (NCC), data coordinating centre (DCC) and a methods core (MC) (figure 2). This structure was established to provide the four clinical trials with support similar to that of a Contract Research Organisation. The iPCT steering committee includes the NCC, DCC, MC, the principal investigators and trial managers for each of the four trials, the TREKK parent advisory group and a parent partner. These newly-formed centralised structures are able to leverage the existing research infrastructure in the emergency departments of the six enrolling sites. These sites have significant and collective experience in conducting multicentre, investigator-initiated clinical trials.

Network coordinating centre

Members of the network coordinating centre (NCC) include the network manager, two paediatricians experienced in clinical trials, a methodologist, a project manager and an administrative coordinator. The NCC meets weekly and is responsible for overseeing the operation of all four clinical trials, including study budgets, training, chairing the steering committee and financial reporting to funding organisations. The NCC is also responsible for the development of standardised templates for protocol writing, start-up training for each study, adverse drug reaction reporting, training logs and data clarification forms.

The legal team at the NCC, in collaboration with legal representation from each participating institution (ie, recruitment site), created a master contract which outlines a partnership arrangement between the participating institutions (figure 3). In addition to the network



Figure 2 Geographical distribution of the iPCT project network across Canada. Four sponsoring institutions (yellow stars), one for each trial, coordinate across six primary recruitment centres (black text) with the NCC in Winnipeg, the DCC in Edmonton and the MC in Toronto. CHRIM, Children's Hospital Research Institute of Manitoba; CHU, Centre hospitalier universitaire; DCC, data coordinating centre; iPCT, Innovation in Paediatric Clinical Trials; MC, methods core, NCC, network coordinating centre; WCHRI, Women and Children's Health Research Institute.

agreement, a template clinical trial agreement was drafted by the NCC to be used to generate individual trial agreements. These vary slightly based on the institutional policies of the four sponsoring research institutes (one for each trial), but each trial agreement outlines conduct and responsibilities specific to the trial hosted at the site.

A further key role for the NCC is the establishment of a centralised Data Safety Monitoring Board (DSMB) with the goal of providing a comprehensive review of study data for all four trials using only one committee, to enhance efficiency. The NCC developed a charter for the DSMB outlining roles and responsibilities, membership, review process and meeting structure. The DCC (described below) provides extensive reporting to the DSMB regarding approach, recruitment and retention for all four studies, as well as specific safety issues regarding procedures and medications, if any. Patient recruitment will be measured against estimated recruitment numbers

needed from the study protocol based on power calculations provided by principal investigators. Over time, the DSMB will advise the iPCT steering committee regarding the merit of continuation of studies based on recruitment and any arising safety concerns. The charter is a living document and can be adapted as needed by the DSMB in conjunction with the iPCT steering committee.

Data coordinating centre

The data coordinating centre (DCC) includes a biostatistician, data scientist, data manager, database developers and team lead for overall project management. The DCC is responsible for the development and support of the clinical trial databases using the electronic data capture tool, REDCap,⁷ for data management, maintenance of the database infrastructure, development and execution of the data management plan, data reporting and query management. In addition, the DCC is supporting

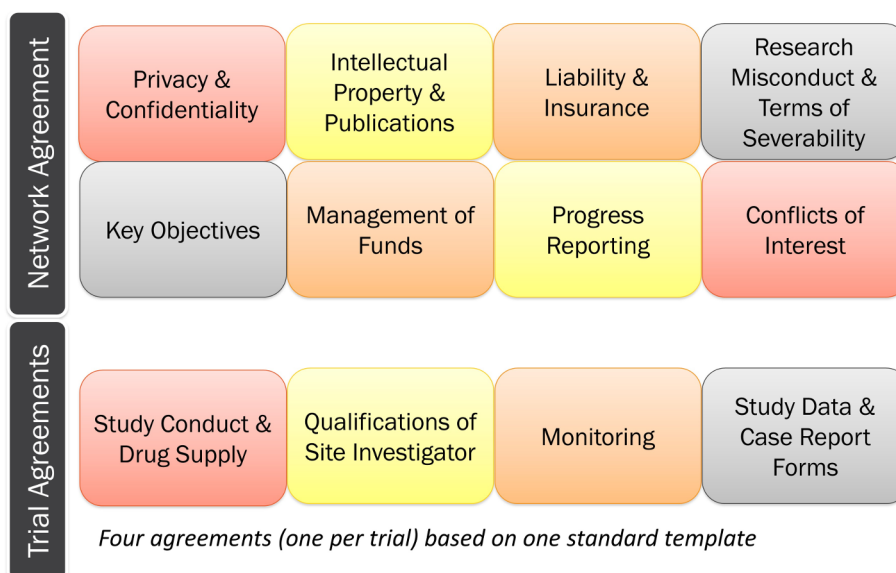


Figure 3 Contents of overarching network agreement and individual clinical trial agreements for the iPCT project. iPCT, Innovation in Paediatric Clinical Trials.

regulatory submissions to Health Canada and trial monitoring in partnership with the quality management in clinical research group at the University of Alberta.

Methods core

The methods core (MC) comprises experts across three institutions and includes two trial methodologists, two health economists, three biostatisticians and a project manager. The MC has supported the trials' protocol development and leads the development of innovation methodology in trial design and statistical analysis for all four trials. Over the coming months, the MC will also develop training modules on aspects of innovative trial design and will be responsible for any interim analyses as well as the final data analysis for each trial. Some innovative methods being applied include the incorporation of Bayesian decision analyses and value of information analysis in trial design, as well as the use of innovative randomisation designs and patient preference elicitation methods in understanding which outcomes are most important to patients, parents, healthcare providers and policy-makers in a clinical trial. The latter is described in more detail under 'Patient engagement' below.

Coordinated operations

The extensive costs of implementing a multicentre drug trial may jeopardise the execution of a high quality study design (ie, compromising to the quality of the data collection or extent of new knowledge achieved as a result of incomplete data accrual). With the goal of eliminating the need for such compromises, our model is intended to significantly reduce costs by (i) initiating four clinical trials over 4 years with overlapping recruitment periods and (ii) avoiding duplication within the sampling frames. Patient arrival in a paediatric emergency department is rarely predicted or planned. Thus, anticipating staffing needs for recruitment of children arriving with a specific medical condition is virtually impossible. Instead, emergency researchers schedule research nurses to match to high volume times in the emergency department. The cost of recruitment personnel is by far the largest budget item in most paediatric drug trials. By sharing this expenditure across four studies, we can reduce the per-patient cost of recruitment by optimising the research nurses' use of time. While competing research nurse priorities for four studies might lead to a small decrease in daily recruitment for any single study, it allows for significant extension of the overall recruitment period. For the purposes of the iPCT project, this allows for more efficient capture of conditions with seasonal variation (eg, bronchiolitis, gastroenteritis and fractures). Furthermore, this staffing pattern alleviates the need to intermittently relieve research staff of their duties in low prevalence seasons, which can be highly disruptive and discourages the retention of highly skilled staff. Finally, study teams can share training costs, site visit coordination, data platforms, statistical support and equipment such as tablets for data collection. Initiating four distinct trials over

a short period requires tremendous cooperation and understanding among principal investigators and trial managers. This is an existing strength within the PERC network, and leveraging this strength is not only helping to achieve the goals of our iPCT project, but it is also something we hope can be passed along to researchers outside of paediatric emergency medicine through the continuing work of KidsCAN Trials.

Long-term sustainability

As mentioned in the Introduction, we leveraged existing research infrastructure (including clinical trial experience and human resources) at the participating institutions to build the centralised management structures and processes described above. Because these trials originated from PERC investigators, the infrastructure is specific to paediatric emergency departments. The long-term goal of KidsCAN Trials is to use the structures and processes emerging from the iPCT project to launch sustainable infrastructure to support paediatric clinical trials across all aspects of paediatric medicine, including such subspecialties as neurology, endocrinology, metabolics and many others. These structures comprise, by necessity, a coordinated network of core supports hosted at multiple academic institutions or research institutes across Canada. **Figure 1** illustrates how the iPCT workflow is intended to build these structures.

Existing networks in other North American and European countries have given us examples to follow (see **box 1** for web links). In the USA, the Paediatric Trials Network is an alliance of cooperating clinical research sites sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and is built on a centralised hub and spoke model. In contrast, and more aligned with our model, the Institute for Advanced Clinical Trials for Children (also in the USA) supports and manages a network of trial-ready sites and collaborates with disease-focused or regional research networks. Similarly, the UK Clinical Research Collaboration oversees and supports a network of registered clinical trial units, some of which house expertise in paediatric clinical trials. Each of the clinical trial units is capable of independently supporting all aspects of the clinical trial, or they have formalised relationships with other groups to meet all trial requirements. Other European countries have similar, coordinated networks of multiple academic institutions or research institutes with government-funded, core support (eg, the Medicines for Children Research Network in the Netherlands, the Finnish Investigators Network for Paediatric Medicines). Our objective is to learn both from these networks and from our national iPCT experience, building also on the experience and expertise of PERC, to grow KidsCAN Trials into a national and sustainable resource to coordinate and streamline paediatric clinical trials in Canada and internationally.

Centralised risk-based safety monitoring

According to Health Canada's interpretation on Good Clinical Practice (GCP) (see Related Links), the purpose

Box 1 Related links**Canadian institutes of health research strategy for patient-oriented research**

- ▶ Innovative Clinical Trials Initiative <http://www.cihr-irsc.gc.ca/e/49773.html>
- ▶ Patient Engagement Framework <http://www.cihr-irsc.gc.ca/e/48413.html>

Partners in the iPCT project

- ▶ Maternal, Infant, Child and Youth Research Network (MICRYN) <http://micryn.ca/>
- ▶ KidsCAN Trials <https://www.kidscantrials.ca/>
- ▶ Paediatric Emergency Research Canada (PERC) <https://www.perc-canada.ca/>
- ▶ Translating Emergency Knowledge for Kids (TREKK) <https://trekk.ca/>
- ▶ Children's Hospital Research Institute of Manitoba (CHRIM) <http://chrim.ca/>
- ▶ George and Fay Yee Centre for Healthcare Innovation (CHI) <https://chimb.ca/>
- ▶ Women and Children's Health Research Institute (WCHRI) <https://www.wchri.org/>
- ▶ The Hospital for Sick Children (SickKids) Research Institute <http://www.sickkids.ca/Research/index.html>
- ▶ Clinical Trials Ontario (CTO) <http://www.ctontario.ca/>

Web links for related networks

- ▶ Paediatric Trials Network (PTN) <https://www.pediatrictrials.org>
- ▶ Institute for Advanced Clinical Trials for Children (I-ACT) <https://www.iactc.org>
- ▶ UK Clinical Research Collaboration (UKCRC) <http://www.ukcrc.org/>
- ▶ Medicines for Children Research Network (MCRN) mcrn.nl/about-mcrn
- ▶ Finnish Investigators Network for Paediatric Medicines (FINPEDMED) www.finpedmed.fi
- ▶ Generation R: Young people improving health through research in the UK <https://generationr.org.uk/>
- ▶ International Children's Advisory Network (iCAN) <https://icanresearch.org/>

Guideline documents and resources

- ▶ Health Canada Guidance Document: Good Clinical Practice https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demanded/guide-ld/ich/efficac/e6r2-step4-eng.pdf
- ▶ European Medicines Agency reflection paper on risk based quality management in clinical trials http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf
- ▶ Canadian Recommendations on Patient Engagement Compensation https://diabetesaction.ca/wp-content/uploads/2018/07/TASK-FORCE-IN-PATIENT-ENGAGEMENT-COMPENSATION-REPORT_FINAL-1.pdf
- ▶ Patient-Centred Outcomes Research Institute (PCORI) Evaluation Framework 3.0 <https://www.pcori.org/sites/default/files/PCORI-Evaluation-Framework-3.0.pdf>

of monitoring is to ensure that (i) trial data are accurate, complete and verifiable, (ii) the trial is being conducted according to GCP and (iii) the rights and well-being of human subjects are protected. The most recent iteration of GCP (ICH E6R2) recommends that clinical trials take a

systematic, prioritised, risk-based approach to monitoring with a documented rationale for the chosen strategy in the monitoring plan. Some regulators, including the Food and Drug Administration (FDA) in the USA and the European Medicines Agency, do not specifically determine clinical trial oversight for sponsors, as there is no one-size-fits-all model (see Related Links for further information). The FDA has outlined justification criteria for developing a risk-based monitoring plan, which are summarised in [table 1](#). Along with the specific activities, monitoring plans should also describe the frequency of monitoring, documentation, management of non-compliance and communication of monitoring results.

For our iPCT project, we have incorporated guidance from both Health Canada and the FDA to take a risk-based approach to our centralised monitoring strategy. As shown in [figure 4](#), our strategy incorporates both centralised data monitoring and on-site monitoring components. On-site monitoring is performed at the recruitment sites, while centralised data monitoring involves a remote evaluation of accumulating trial data. Centralised data monitoring carries the advantage of providing routine data review in real time and standard checks for data consistency, completeness and accuracy across sites, but it may not identify all risks to trial integrity such as ensuring investigators are only enrolling participants meeting all eligibility criteria (see FDA guidance document under Related links for further information). We accept these parameters based on the experience of our clinical investigators and the fact that the medications studied are, for the most part, already used commonly to manage paediatric conditions.

Monitors are typically appointed by the sponsoring (primary) institution. The uniqueness of the iPCT project lies in the use of bilingual, centralised monitoring so that the four trials, conducted in parallel at six enrolling sites in Canada, can share monitoring resources. This allows individual sites that do not have the existing institutional resources to provide monitoring to be included. The shared resource is facilitated in part by the mandate of the University of Alberta, one of our trial sponsors, to provide its principal investigators with monitoring across all sites. With the help of this provision, we have recruited independent monitors, fluent in both English and French who will monitor all four trials in parallel, to increase the efficiency of on-site visits. Our monitors therefore have documented qualifications and demonstrated capabilities to ensure the trial is conducted appropriately in both of Canada's official languages.

Ethical review

Attaining research ethics board (REB) approvals with any efficiency is one of the main operational challenges for multicentre clinical trials in Canada, particularly those that span multiple provinces. In Canada, there is no nation-wide standardised operational guidance to the ethical review of health research, though a call for one has been published recently.⁸ Individual REBs vary in

Table 1 Risk factors to consider when justifying centralised data monitoring and on-site monitoring using a risk-based approach to monitoring clinical trials. Source: Food and Drug Administration (see related web links for further detail)

Factor	Rationale for justification
Complexity of study design	More intensive monitoring may be required for studies with adaptive designs, complex dose titrations or multiple device placements.
Types of endpoints	Subjective endpoints may require more on-site visits to ensure consistency. Objective endpoints (eg, death, lab values) may be more suitable for centralised data monitoring.
Clinical complexity of population	Seriously ill or vulnerable populations may require more on-site monitoring to ensure appropriate protection.
Geography	Standards of medical practice may vary between regions. Sites with less established CT infrastructure may require more frequent on-site monitoring.
Experience of PI and sponsor	Increased monitoring may be required on principal investigators or sponsors who lack significant CT experience or have previously failed regulatory audits.
Electronic data capture	Centralised data monitoring can capture real-time quality metrics, such as missing data, data errors or protocol violations to identify high-risk sites for on-site monitoring.
Safety of intervention	Tapered approach may be required with increased monitoring early on until preliminary safety data has been reviewed.
Quantity of data	Centralised data monitoring may be more useful for large trials with multiple sites and long duration.

CT, clinical trial; PI, principal investigator.

their approval requirements, and as a result, the ethics approval process for national, multicentre trials is inefficient, redundant, costly and burdensome to individual sites.⁴

Separate from our iPCT project, and to address these challenges on a provincial level, the Ontario Ministry of Economic Development and Innovation established the not-for-profit Clinical Trials Ontario (CTO) in 2012. CTO’s mandate, accomplished through the CTO Streamlined Research Ethics Review System, is to serve as a single provincial ethics review for multicentre clinical trials within the province of Ontario. It has been successful in enhancing the efficiency and consistency of the ethical review and approval process (see Related Links for more information). Investigators who are submitting trials to

CTO complete a web-based standardised application form and are provided with a CTO-approved consent template. Applications are then reviewed by a CTO-qualified Board of Record, and delegated reviews occur at study sites.

For the purposes of our iPCT project, we have been able to leverage the Ontario effort at least partially. Two of the iPCT clinical trials are led by principal investigators residing in Ontario. They have a CTO-qualified REB and thus can serve as the Board of Record for the iPCT trial initiated by the investigator at these Ontario institutions. Once the trial is approved by CTO, individual REB applications are still required at participating institutions in Ontario, but these reviews are expedited and primarily administrative. The reciprocal agreement between CTO-approved REBs has resulted in a consistent

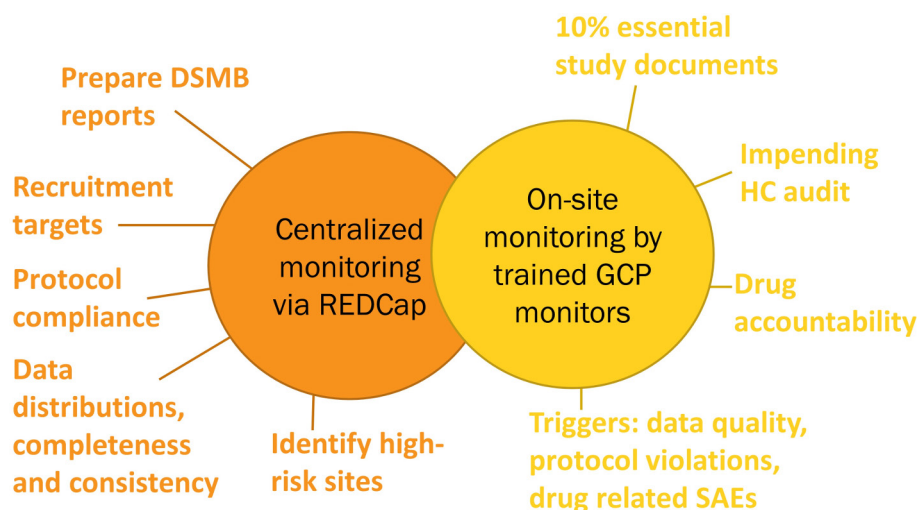


Figure 4 Centralised, risk-based monitoring approach used in the iPCT project. DSMB, datasafety monitoring board, GCP, Good Clinical Practice; HC, Health Canada; iPCT, Innovation in Paediatric Clinical Trials; SAE, serious adverse event.

and timelier approval process, with a consistent consent form and letter of information across the Ontario sites. The four recruitment sites for the iPCT project that are located outside of the province of Ontario do not currently have a reciprocal relationship with CTO, and thus institution-specific REB approvals are still required for these sites. However, at the time of writing the University of Manitoba has agreed to recognise the CTO REB approval and will allow an expedited review in Winnipeg (rather than a full board review). The experience gained from our iPCT project, building on the success of the Ontario CTO effort, will not only assist the PERC network in conducting future research, but will also better equip MICYRN to work towards a nationally coordinated ethics approval effort.

Another important consideration in setting up a multi-institutional REB approval process is assent. Assent is sought from children who are too young to fully comprehend the risks and benefits of participation but old enough to follow study-related tasks. Obtaining assent serves to empower children by allowing them to participate in the decision-making process. Most REBs require that assent be sought through a paper document signed by the child or adolescent following consent by the caregiver.⁹ The content of the assent form mirrors that of the letter of information provided with the consent form to preadolescent children. REBs can waive the requirement for assent based on the intellectual capacity of the child or the magnitude of direct benefit to participation.⁹ There is no predetermined age of consent in Canada, and thus the ability to obtain consent in a clinical research setting is predicated on establishing that the individual can comprehend the risks and benefits (if any) of participation. It also helps to ensure their potential concerns are communicated to research teams.

There is currently no consensus on the 'operational and construct definitions' of assent in children, nor is there any standardised governance regarding from whom assent should be sought. As a result, assent forms and policies are often institutionally heterogeneous and, furthermore, are easily conflated with caregiver consent.¹⁰ For example, each of the six iPCT enrolling sites (with one exception) had a unique REB-driven approach to the assent form. Differences in the information contained in assent forms across sites could theoretically pose difficulties with recruitment and compliance. To overcome this limitation, we developed a common assent template for the iPCT project, based on the existing institutional forms available. The common template was then presented to a parent focus group (provided by the TREKK network, described under 'Partnerships' above) and their children, who provided valuable insight. At the time of writing, CTO (which has an established consent template) has the iPCT assent template under review for potential province-wide implementation in Ontario, which demonstrates the influence of projects like iPCT on provincial and federal jurisdictions. Policies surrounding the age of assent and

mature consent are still variable across sites and further efforts for harmonisation are warranted.

Patient engagement

A central tenet of the iPCT project, as part of Canada's Strategy for Patient-Oriented Research, is the meaningful engagement of patients (children and youth) and their parents and families. Meaningful engagement is defined as active collaboration with patients and families in the governance, priority-setting, research conduct and dissemination of results to help ensure that the research will be relevant, appropriate and sensitive to the real-world context of patients and caregivers.¹¹ When applying for funding, the iPCT project engaged a parent partner as a 'principal knowledge user' on the application. This individual is now a member of the iPCT steering committee and provides unique insight on deliverables, such as reviewing study protocols to ensure designs are responsive to the needs of participants.¹² Steering committee members participated in an introductory session about patient engagement in health research, which included instruction on creating safe spaces¹³ and the different types of participatory approaches needed to gain consensus as a group. Since then, advisors from both the TREKK parent advisory group and the CHI patient engagement platform have been accessed by our network members in setting up and conducting the iPCT clinical trials. Our parent partner will also work with the steering committee to recruit parent partners at each of the other recruiting sites.

The approach to recruitment and enrolment of participants in clinical trials will be one area of focus for patient engagement. The emergency department can be a stressful, painful and even traumatic experience for families and participation in research may not be seen as a priority.^{14 15} Philosophically, patients who are the end-users of healthcare are the best source of information when seeking the most sensitive and effective way to approach patients and families in the emergency department for potential enrolment in a trial.¹⁶ Recruitment strategies and study materials for the iPCT trials are being co-developed with patients and families to help ensure (i) that researchers are sensitive to the realities faced by families in the paediatric emergency department, (ii) that the language and content is accessible to potential study participants and (iii) that questions posed by potential participants about the study are addressed in a way that is understandable,¹⁷ culturally sensitive and trauma-informed.

We also understand the importance of compensating external lay partners for their valuable contribution and provide an honorarium for meeting participation. Researchers in Canada are becoming increasingly aware of the need to compensate lay partners (ie, non-academics) for any expenses incurred (eg, travel, child care) while partnering in research decision-making (see Related Links for more information). There is also an increasing awareness of the value of the experiential

knowledge of public partners, demonstrated by the recognition of, and financial compensation for, the contribution of time, energy and expertise¹⁸ by members of the lay public. However, guidelines in Canada on compensation are broad, and there are different compensation regulations across the provinces, making it difficult to apply a consistent approach. We intend for the iPCT project to set a national example and contribute to the discussion about standards and guidelines.

To determine the effectiveness and utility of the proposed patient engagement strategies, a mixed-methods evaluation approach will be applied annually as part of the iPCT project outcomes. Our approach is modelled after various sources, including other advisory networks such as the International Children's Advisory Network, the UK-based Generation R and the US-based Patient-Centred Outcomes Research Institute. Online surveys and one-on-one interviews with patient or parent partners, researchers and other network members are being designed to help inform (i) the quality of engagement activities (eg, Do patient partners feel heard and valued? Do researchers respect the experiential knowledge contributed by patient partners? How are disagreements and conflicts resolved?), (ii) the level of engagement and participatory approaches chosen (eg, Does the participatory approach that we use help us come to a consensus on research decisions?) and (iii) the impact of engagement (eg, on the research project, on the researchers, on the patient partners).^{19 20}

Parent partners have also played a pivotal role in the study design. One of the trials in the iPCT project is using a novel preference-informed complementary trial design. This approach is built around two simultaneous trials to maximise participation, optimise cost-effectiveness and allow for a qualitative exploration of the reasons behind caregiver decision-making. Because this novel trial design allows for the caregivers of study participants to choose which of two trials they wish to participate in, parent involvement in trial and survey tool design was critical. One parent representative has been involved from the outset, informing the development of research methods, case report forms and scripts for research staff who will be approaching families for recruitment. Her presence at team meetings, both via teleconference and in person, allows for the application of a unique family-centred, non-clinical lens to the planning of the study. Notably, her insight has informed more sensitive and family-centred wording for our surveys. A parent advisory group is also informing the development of the qualitative portions of the study, where we seek to understand caregiver reasoning for medical decisions regarding drug choices. In this manner, we are able to ensure that our results reflect and capture what matters to families.

Challenges and solutions

The establishment of the iPCT infrastructure was not without obstacles. The team encountered specific implementation challenges pertaining to budget and

operations. Long delays in legal negotiations were eventually resolved by a teleconference among legal representatives from all involved parties which assisted the contract process. However, these delays in the partnership agreement carried over to the transfer of funds to participating institutes, postponing the hiring of dedicated research team members. Fortunately, the principal investigators for each of the four trials were able to engage the support of existing research staff to support protocol development.

An additional lesson learnt was in the identification of a manufacturing process for placebo study formulation. Several companies provided quotes which far exceeded the initial budget estimates. Eventually, the College of Pharmacy at the University of Manitoba was engaged to create the oral elixir placebo formulations and complete stability testing as required for the clinical trials application. Each site can now formulate both the active and placebo compounds in their local pharmacy. This is aligned with compounding which already occurs at the involved paediatric centres. On-site formulations by experienced research pharmacies has allowed for significant savings in both product and shipping fees, and the development of new academic partnerships.

CONCLUSIONS

Our iPCT project represents the first joint venture between an existing specialised paediatric research network (PERC) and a centralised clinical trial management system (KidsCAN Trials) in Canada. In this project we are implementing innovative, cost-saving and patient-centred operational methods to conduct multiple clinical trials in parallel across six hospitals in four Canadian provinces. While paediatric clinical trial networks exist in other jurisdictions such as the USA and Europe, KidsCAN Trials is one of the first collaborations in Canada to support multidisciplinary research in the safe and effective use of pharmaceuticals in children. We learnt a great deal about process and operations of managing multiple academic sponsors with regulatory quality clinical trials across multiple jurisdictions and centres. The impact of this collaboration on the feasibility and trial quality will be evaluated prospectively and used (i) to assist PERC and other paediatric research collaborations in the future and (ii) to inform future KidsCAN Trials initiatives. We look forward to achieving both aims and to contribute to the international paediatric clinical research community.

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