



Study Design

The Canadian Pediatric Cardiology Research Network: A Model National Data-Sharing Organization to Facilitate the Study of Pediatric Heart Diseases

Frédéric Dallaire, MD, PhD,^a Marie-Claude Battista, PhD,^b Steven C. Greenway, MSc, MD,^c Kevin Harris, MD, PhD,^d Emilie Jean-St-Michel, MD, MSc,^e and Andrew S. Mackie, MD, SM;^f on behalf of the Canadian Pediatric Cardiology Research Network members[‡]

^a Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, and Université de Sherbrooke, Sherbrooke, Québec, Canada

^b Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Québec, Canada

^c Departments of Pediatrics, Cardiac Sciences and Biochemistry and Molecular Biology, Alberta Children's Hospital Research Institute, Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

^d BC Children's Hospital, Vancouver, British Columbia, Canada

^e Hospital for Sick Children, Toronto, Ontario, Canada

^f Stollery Children's Hospital, Edmonton, Alberta, Canada

ABSTRACT

Background: Common hurdles to pediatric cardiology research include the heterogeneity and relative rarity of specific cardiac malformations, the potential for effect of residual lesions occurring decades after repair, and the scarcity of objective and easily measurable outcomes such as death and transplantation.

RÉSUMÉ

Contexte : Les obstacles courants dans le domaine de la recherche en cardiologie pédiatrique comprennent l'hétérogénéité et la rareté des malformations cardiaques, le fait que des lésions résiduelles aient des répercussions qui se manifesteront des décennies après une intervention, et la rareté des issues cliniques objectives et

Congenital heart disease (CHD) affects 1%-2% of children and is responsible for more than a quarter of all deaths in children.^{1,2} In the United States, CHD is the primary diagnosis in 4% of all hospitalizations in children but is responsible for 23% of hospital costs.^{2,3} In Canada, infants with severe CHD have hospitalization rates 20 times greater than those without CHD.^{4,5} As with other pediatric subspecialties, the generation of large-scale, robust scientific evidence in pediatric cardiology to guide clinical practice has unfortunately lagged behind that of adult cardiovascular diseases (eg,

systemic hypertension, heart failure, and atherosclerosis).⁶ Despite this, significant progress has been made in the care of children with CHD, yet treatment of CHD is often on the basis of low-quality or “eminence-based” evidence.

The common barriers to CHD research have long been recognized.^{7,8} Although overall CHD is the most common congenital malformation, there is tremendous heterogeneity and many specific cardiac malformations are individually rare. Furthermore, symptoms and complications can manifest many years after birth or surgical repair. Because of improvements in medical and surgical management over the past 5 decades, objective and easily measurable outcomes such as death and transplantation are now relatively rare in childhood. The establishment of large multi-institutional cohorts is thus needed. However, collaborations that cross provincial boundaries and health care jurisdictions can be difficult to establish and maintain.

To improve data quality, patient outcomes, and quality of life for children with CHD, it is imperative that experience, expertise, and data be pooled and shared. In 2017, the Canadian Pediatric Cardiology Association, an affiliate of the Canadian Cardiovascular Society, prioritized the creation of a

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Ethics Statement: The CPCRN adhere to the Canadian tricouncil policy statement on the ethical conduct for research involving humans.

[‡]The complete list of the members of the Canadian Pediatric Cardiology Research Network is provided in Supplemental Table S1.

Corresponding author: Dr Frédéric Dallaire, Department of Pediatrics, Université de Sherbrooke and Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, 3001, 12e Avenue Nord, Sherbrooke, Quebec J1H 5N4, Canada. Tel.: +1-819-346-1110 x70454.

E-mail: frederic.a.dallaire@usherbrooke.ca

See page 514 for disclosure information.

Methods: To help meet these challenges, the Canadian Pediatric Cardiology Research Network (CPCRN) was founded by the Canadian Pediatric Cardiology Association to link Canadian academic institutions to promote and facilitate multicollaborations for the benefit of pediatric and congenital cardiology research. The overarching goal of the CPCRN is to build a national framework that harnesses the strong desire for collaboration within the pediatric cardiology community and to identify solutions to barriers that impede multicentre partnerships.

Results: In this report, the authors describe the approach and the components of the CPCRN. Specifically, we detail the rolling out of a pan-Canadian master agreement that covers current and future studies, the systematic banking of all project data, and the mechanisms developed to facilitate secondary use of data.

Conclusions: This experience could help guide the formation of other national research groups, particularly those focused on congenital or rare diseases.

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Méthodologie : Pour remédier à ces obstacles, le Réseau canadien de recherche en cardiologie pédiatrique (CPCRN) a été fondé par la l'Association canadienne de cardiologie pédiatrique afin de mettre en relation les établissements universitaires canadiens et de promouvoir ainsi des collaborations multiples qui bénéficieront à la recherche en cardiologie pédiatrique et congénitale. L'objectif principal du CPCRN est de mettre sur pied une structure nationale qui tire profit de l'important désir de collaboration dans le domaine de la cardiologie pédiatrique et de trouver des solutions aux obstacles qui nuisent aux partenariats entre les différents établissements.

Résultats : Dans cet article, les auteurs décrivent l'approche et les composantes du CPCRN. Ils passent en revue les détails du déploiement d'une entente-cadre pancanadienne concernant les études en cours et à venir, la mise en banque systématique de toutes les données de recherche et les mécanismes mis au point pour permettre l'utilisation secondaire de ces données.

Conclusions : Cette expérience pourrait permettre de guider la formation d'autres groupes de recherche nationaux, plus particulièrement dans les domaines des maladies rares ou congénitales.

pan-Canadian research network. The overarching goal was to build a national framework that harnessed the strong desire for collaboration within the pediatric cardiology community and to identify solutions to barriers that impede multicentre partnerships. To serve this purpose, we founded the Canadian Pediatric Cardiology Research Network (CPCRN; Fig. 1).⁹ In this report, we describe the aims and components of the CPCRN, which can serve as a model organization to link geographically distant academic centres to the benefit of rare pediatric disease research.

Methods

Objectives

The overarching aim of the CPCRN is to foster research collaborations across Canada and across institutional boundaries to achieve advances in pediatric heart disease through the conduct of multi-institutional studies. The specific objectives of the CPCRN are to:

- Build a network of Canadian physicians and researchers in pediatric cardiology
- Identify shared national research interests in pediatric heart diseases
- Establish and test efficient and flexible ways of developing and implementing multicentre research projects in Canadian pediatric institutions

- Create and maintain a secure national data repository to improve data standardization and facilitate secondary use of research data
- Develop and test a transparent and structured approach to determine data ownership and fairly acknowledge individual contributions
- Contribute to the standardization of research ethics boards (REB) requirements and facilitate interprovincial recognition.

Overview of the CPCRN structure

An overview of the governance structure of the CPCRN is presented in Figure 2. The CPCRN is led by a scientific director supported by a national Steering Committee composed of individuals from across Canada representing small-, medium-, and large-volume congenital cardiac centres. The CPCRN's administrative services, coordination and Data Center are managed by the Scientific Director. The Scientific Director and Steering Committee member positions are voluntary appointments to be held by a CPCRN Member affiliated with a Canadian institution. The CPCRN coordinator works closely with the Scientific Director and is responsible for the day-to-day communications with members and for providing logistical and scientific support for CPCRN studies. The CPCRN is currently hosted at the Centre de Recherche du CHUS in Sherbrooke, Canada.

CPCRN membership comprises pediatric cardiology researchers and clinicians affiliated with a Canadian institution that provides medical care to children with heart disease. Any CPCRN-affiliated member can propose a new research initiative to the CPCRN. The Steering Committee is then responsible to ensure that the proposed research project aligns with the CPCRN's objectives, is well designed and of high scientific value, is feasible, and is compatible with ongoing or pending projects.

The CPCRN assists members by providing administrative, logistic, and scientific support at each step of the research process (ie, protocol development, REB review, contract negotiation, enrollment of study sites, data collection, data management, safe data repository, data analysis, and research



Figure 1. Bilingual logos of the Canadian Pediatric Cardiology Research Network.

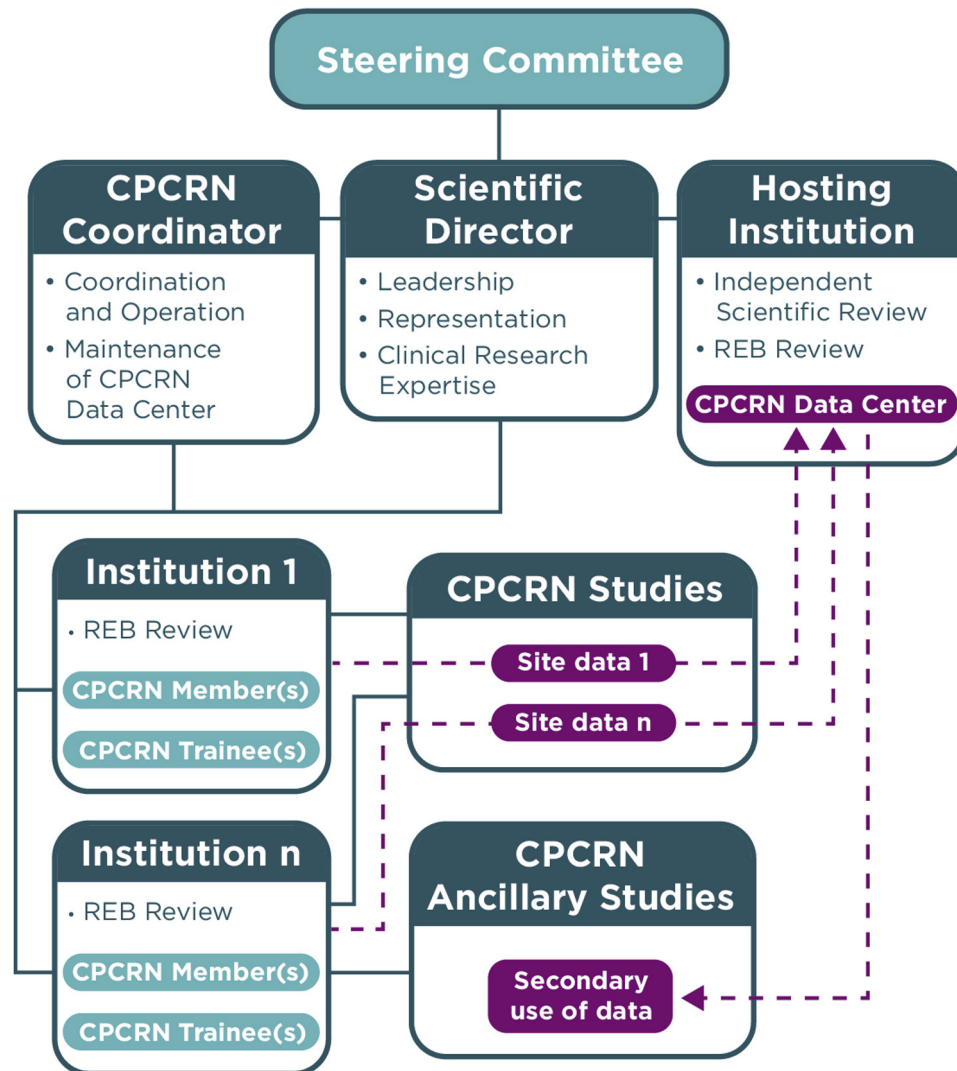


Figure 2. Overview of the Canadian Pediatric Cardiology Research Network (CPCRN) governance structure.

dissemination). Furthermore, a standardized data-banking approach is in place to facilitate future secondary use of all collected research data.

Study proposal flow

Research projects are proposed by a CPCRN member who becomes the principal investigator. There is no restriction on the study design and the studies can be observational, experimental, evaluative, prospective, or retrospective. Each project is reviewed by the Steering Committee on the basis of feasibility, alignment with the CPCRN objectives, scientific merit, and potential effect on the health of children with heart diseases. When the project is approved, the Scientific Director and Steering Committee members work with the principal investigator to develop the proposed project into a full study protocol. The CPCRN contributes synergistically to project development by providing scientific, methodological, biostatistical, and data management support to the study team. The final study proposal is then presented to all CPCRN members to identify participating centres. If there are a sufficient

number of interested sites to reach the targeted sample size, then the proposal is put forward for approval by individual REBs at each participating institution.

A unique innovation: a national data-sharing agreement

Multi-institutional and multijurisdictional studies are complex and often seen as unappealing because of the need for multiple bilateral data-sharing agreements between each institution that must be negotiated anew for each new project. Furthermore, these agreements might differ between institutions for a given project, which often complicates or even prohibits the secondary use of valuable research data.

We designed and implemented a unique master agreement that covers respective responsibilities, data ownership, data-sharing, and confidentiality matters across provincial and institutional boundaries. Thanks to this national agreement, new CPCRN studies are automatically covered, which avoids repeated and lengthy renegotiation of multiple bilateral agreements. Because of its uniformity and broad reach, this master agreement covers most aspects of data-sharing and data

ownership in a homogenous fashion across study sites. We envision that having a national master agreement will decrease time to study initiation, reduce resources spent negotiating elements that remain similar across studies, improve participation rates, and facilitate access to data for secondary analysis.

Interjurisdictional integration of research ethics

In the Canadian tricouncil policy statement on the ethical conduct for research involving humans, alternative models are proposed for REB review and oversight of projects involving several institutions. These models “[...] are intended to provide flexibility and efficiency, and avoid unnecessary duplication of review without compromising the protection of participants.”¹⁰

There are some structures in place to simplify and centralize multi-institutional REB reviews within provinces. Nevertheless, much remains to be done to improve interjurisdictional integration of research ethics evaluations. The CPCRN aims to contribute to advances in REB cross-recognition by associating with important Canadian initiatives such as the Canadian Collaboration for Child Health: Efficiency and Excellence in the Ethics Review of Research (CHEER).¹¹ The oversight, consistency, and transparency offered by the CPCRN in initiating and conducting research projects will be valuable in moving forward with more flexible and yet efficient ways of ensuring that research ethics standards are met.

Data banking and ownership

The CPCRN aims to encourage and facilitate the secondary use of research data, which increases the value of collected data without increasing the risk to participants. The concept of a generalized data-banking approach to facilitate secondary analyses and promote unburdened data access is embedded within the CPCRN structure and the master agreement. Research data for all projects is deidentified and banked to remain accessible for secondary use. To do this, the process of data banking must remain an integral part of all study protocols, REB applications, and informed patient consent to ensure that the appropriate level of approval is given by the study participants, institutions, and governing bodies.

The CPCRN Data Center is under the responsibility of the Scientific Director together with scientific oversight from the Steering Committee. Data from individual sites remains accessible to the CPCRN members who originally contributed the data. Pooled and deidentified data are available to CPCRN members for secondary analyses upon request and after scientific and REB approval of the hosting institution.

At present, all CPCRN data are hosted at the Centre de Recherche du CHUS. The Research Electronic Database and Capture (REDCap)¹² data management system software is hosted on secure servers of the Collaborative Research for Effective Diagnostic group within the informatics infrastructure of the Centre de Recherche du CHUS. These servers are certified by the Quebec Ministry of Health and Social Services to hold confidential health information. These servers comply with the certification requirements of applications implemented on the Réseau intégré de télécommunications multimédia du Québec as well as with the International

Organization for Standardization/International Electrotechnical Commission 27001 standard for information security management systems.

Contribution and authorship

The process of recognizing intellectual contributions and determining authorship is predetermined and clearly defined (see the *Publication and Authorship* section of the [Supplemental Material](#)). It is on the basis of original scientific contribution (project idea and study design), data contribution, data analysis, manuscript preparation, and scientific participation. We have deliberately placed the objective of advancing knowledge in CHD before the advancement of individual academic careers. Hence, it is understood that banked data belongs collectively to the CPCRN and not to specific CPCRN members or sites. There is no specific ownership of deposited data that would require a systematic attribution of authorship for data to be used in future secondary analyses. However, the CPCRN is to be included as a coauthor in each publication and the full list of CPCRN members will appear in the footnote or as a supplemental material, depending on the journal's policy. In all cases, the publication of study results and the determination of authorship will follow the recommendations of the International Committee of Medical Journal Editors.¹⁵

Knowledge translation

The CPCRN will serve as a hub to support members with the development of project-specific integrated and end-of-grant knowledge translation (KT) plans with the objective being to generate research that leads to changes in practice. The CPCRN will advise on resources to support members with the development and implementation of their KT plan by building on natural partnerships with the Canadian Cardiovascular Society and the Canadian Pediatric Society. We will also leverage member involvement with local, provincial, and national associations, expert committees, and stakeholders (eg, patient advocacy groups). Because knowledge generated jointly has a better chance of being implemented, the CPCRN will foster early collaboration between key research partners (eg, decision-makers, scientists, clinicians, patients, advocates, community members, and industry) and network members. The main message to be delivered will be adapted to the different stakeholders, and transmitted in a time-efficient manner using various dissemination strategies to ensure that team members will be informed of project progress or that results be disseminated to the largest audience. Each KT plan will be carefully developed to ensure that the study will receive the attention it deserves and that it can be leveraged for future progress.

Results

As of September 2020, 42 individual members from 13 institutions in Canada have joined the CPCRN (Fig. 3). In the pilot phase of the CPCRN, 6 multicentre research projects have been initiated. Five are currently under way and 1 is awaiting financing. The ongoing projects have so far generated data on > 50,000 study participants. These data are held in the CPCRN Data Center and is easily available for secondary analyses.

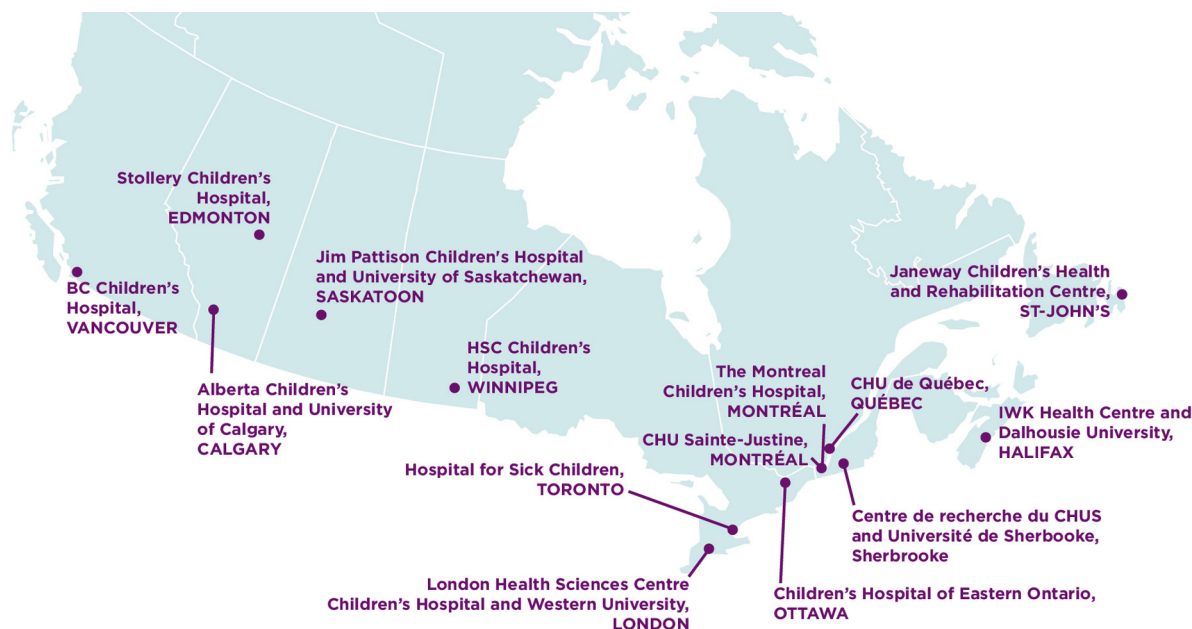


Figure 3. Geographical distribution of the Canadian Pediatric Cardiology Research Network (CPCR) centres.

The CPCR has served as a catalyst to increase the success rate of research financing by CPCR members by increasing the feasibility of cross-provincial, multicentre projects. Thus far, 3 projects have obtained financing, in part by leveraging the expertise and support of the CPCR.

Discussion

The CPCR is the first formal national research network within pediatric cardiology in Canada. However, we recognize that organizing research under the umbrella of a pan-Canadian research network is not new. Several successful research networks with the Canadian pediatric research community have been established previously including Pediatric Emergency Research Canada.¹⁴ Pediatric cardiology investigators outside of Canada have also developed successful networks to increase research capacity, facilitate site enrollment, and coordinate research efforts. One outstanding example is the Pediatric Heart Network,¹⁵ which has generated landmark, multicentre studies.^{16,17} Our approach has been innovative by incorporating most aspects of data-sharing within a single master agreement, embedding systematic research data banking, and by designing an agreement that applies to current and future projects.

Sustainability and financial resources of the CPCR are foreseeable challenges, as for all multicentre research organizations. The pilot phase of the CPCR has relied on generous contributions from provincial foundations as well as from individual institutions. Going forward, we aim to establish a hybrid model with financial resources coming from grant support directed to the CPCR and through a cost recovery model from projects initiated within the CPCR.

In summary, the CPCR will enhance collaboration, facilitate the implementation of multicentre studies, and increase the secondary use of research data. This will enable timely, high-quality, and generalizable research that will

improve care for pediatric patients with CHD. Furthermore, previously understudied research questions will become feasible because of the multicentre and larger-scale approach of the CPCR. Finally, we anticipate that our KT strategy will improve research effects and accelerate the uptake of novel, evidence-based data.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2020.11.014>.