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The Canadian Preterm Birth Network: a study protocol for improving outcomes for preterm infants and their families

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Abstract:	Background: Preterm birth (PTB), birth before 37 weeks of gestation, occurs in ~8% of pregnancies in Canada. It is associated with high mortality and morbidity rates that significantly impact families and the healthcare system. Our overall goal is to create a transdisciplinary platform, the Canadian Preterm Birth (PTB) Network, where investigators, stakeholders, and families will work together to improve childhood outcomes of preterm neonates. Methods: Our national cohort will include 24 maternal-fetal/obstetrical

	units, 31 neonatal intensive care units and 26 neonatal follow-up programs across Canada with planned linkages to provincial health information systems. Three broad clusters of projects will be undertaken. Cluster 1 will focus on quality improvement efforts that use the Evidence-based Practice for Improving Quality methodology to evaluate information from the PTB Network database and review the current literature then identify potentially better health care practices and implement identified strategies. Cluster 2 will assess the impact of current practices and practice changes in maternal, perinatal, and neonatal care on maternal, neonatal and neurodevelopmental outcomes. Cluster 3 will evaluate the impact of PTB on families and health care systems by integrating PTB Network data, parent feedback and national and provincial database information in order to identify areas where more parental support is needed, and also generate robust estimates of resource utilization, cost and cost effectiveness around preterm neonate care. Interpretation: These collaborative efforts will create a flexible, transdisciplinary, evaluable, and informative research and quality improvement platform that supports programs, projects, and partnerships focused on improving outcomes of preterm neonates.

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The Canadian Preterm Birth Network: a study protocol for improving outcomes for preterm infants and their families

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***Group Information:** A complete listing of Canadian Preterm Birth Network Investigators is provided in Appendix 2.

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ABSTRACT

Background: Preterm birth (PTB), birth before 37 weeks of gestation, occurs in ~8% of pregnancies in Canada. It is associated with high mortality and morbidity rates that significantly impact families and the healthcare system. Our overall goal is to create a transdisciplinary platform, the Canadian Preterm Birth (PTB) Network, where investigators, stakeholders, and families will work together to improve childhood outcomes of preterm neonates.

Methods: Our national cohort will include 24 maternal-fetal/obstetrical units, 31 neonatal intensive care units and 26 neonatal follow-up programs across Canada with planned linkages to provincial health information systems. Three broad clusters of projects will be undertaken. Cluster 1 will focus on quality improvement efforts that use the Evidence-based Practice for Improving Quality methodology to evaluate information from the PTB Network database and review the current literature then identify potentially better health care practices and implement identified strategies. Cluster 2 will assess the impact of current practices and practice changes in maternal, perinatal, and neonatal care on maternal, neonatal and neurodevelopmental outcomes. Cluster 3 will evaluate the impact of PTB on families and health care systems by integrating PTB Network data, parent feedback and national and provincial database information in order to identify areas where more parental support is needed, and also generate robust estimates of resource utilization, cost and cost effectiveness around preterm neonate care.

Interpretation: These collaborative efforts will create a flexible, transdisciplinary, evaluable, and informative research and quality improvement platform that supports programs, projects, and partnerships focused on improving outcomes of preterm neonates.

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INTRODUCTION

Preterm birth (PTB), defined as birth occurring before 37 weeks gestation, occurs in approximately 8% of pregnancies in Canada,(1) and has a life-long impact on individuals, their families, and society. As the leading cause of infant death, cerebral palsy, and disability, PTB is estimated to cost the Canadian healthcare system over $8 billion per year.(2) Our previous studies showed that by applying collaborative, integrated quality improvement (QI) via networking, the incidence of major neonatal morbidity such as retinopathy of prematurity, necrotizing enterocolitis and nosocomial infections decreased by 20-50% in preterm infants at <29 weeks' gestational age (GA).(3-5) Outcome improvements to date used our existing platforms, which were limited to neonatal and neonatal follow-up researchers, despite mounting evidence that events before and during pregnancy can have life-long implications for the fetus and child. Furthermore, our platforms were missing data regarding family integration in PTB care, which can also positively affect neonatal outcomes. Thus, the Canadian Preterm Birth (PTB) Network described in this protocol aims to expand and build on our existing neonatal platforms to develop a pan-Canadian network consisting of a transdisciplinary team with expertise in maternal fetal medicine (MFM), obstetrics (OB), neonatology, pediatrics, neonatal follow-up, epidemiology, health economics, and health informatics and also including parents, nurses, other allied healthcare professionals, national/provincial organizations, and policy makers. The primary goal of the PTB Network is to translate knowledge generated by clinical, QI, and health services research into optimal PTB care practices and policies that substantially improve both short and long-term outcomes. In this protocol, we describe the use of this PTB

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Network to implement and assess QI; evaluate the impact of maternal, neonatal, and developmental interventions; and generate estimates of the economic impact of PTB.

METHODS

Overview

The PTB Network will expand the efforts of the existing neonatal networks affiliated with the Canadian Neonatal Network (CNN). CNN collects and maintains data from all 31 Level 3 neonatal intensive care units (NICUs) in Canada and is used for benchmarking, collaborative research, QI, training, and advocacy.(3-8) An internal audit has confirmed that the CNN database is valid and reliable.(9) Furthermore, robust linkages exist between CNN and its associated databases: the Canadian Neonatal Follow-Up Network,(10) the Canadian Neonatal Transport Network, and the Canadian Pediatric Surgery Network.(11) The PTB Network will incorporate all of these existing networks and expand to include the MFM/OB community within 24 tertiary perinatal units across Canada (Figure 1). In addition, we plan to develop linkages with the following databases: BORN Ontario,(12) Nova Scotia Atlee Perinatal,(13) Alberta Perinatal Health Services,(14) BC Perinatal Data Registry,(15) Québec Pregnancy Cohort,(16) and Perinatal Program Newfoundland Labrador(17;18) for obtaining outcomes and health services utilization data during early childhood, and information on the social determinants of health for all preterm infants.

Study population

We will include all preterm births occurring between January, 2018 and December, 2020. Due to the large number of PTBs in Canada, infants will be stratified into three groups based on GA: <29 weeks GA; 29 to 33 weeks GA; and 34 to 36 weeks GA. The PTB Network will initially

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focus on births occurring <29 weeks GA as these infants utilize the most resources and are at the highest risk for adverse outcomes.

Planned activities

The transdisciplinary PTB Network team will use collected data to execute research projects in each of three integrated research clusters described below. The PTB Network research program is designed to be flexible and allow for new projects, project modification, collaborations, and partnerships. The PTB Network Clusters will function as a platform for ongoing integrated comparative effectiveness research, randomized controlled trials, translational studies, proof-of-concept studies, health services evaluation, and programmatic evaluations.

Cluster 1: Evidence-based QI with outcomes

Canadian initiatives using the Evidence-based Practice for Improving Quality (EPIQ) method led to a significant improvement in neonatal outcomes.(3-5) To build on those improvements, the PTB Network protocol will expand the use of EPIQ methods to MFM/OB care practices and the integration of family members in neonatal care. EPIQ methods will be used to conduct QI projects following the Promoting Action on Research Implementation in Health Services (PARIHS) framework of evidence, context and implementation.(19) Using this framework, transdisciplinary investigators at each site who are trained to conduct bi-annual plan-do-study-act cycles(20;21) will identify QI strategies of interest using local data and best-available knowledge in perinatal-neonatal care, implement selected QI activities, and develop and collect process indicator information pertaining to their QI cycles. The PTB Network will provide sites their outcomes bi-annually; the sites will identify changes in their performance over time and compare

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their performance to the national benchmark. Each center will have flexibility to adapt and choose the QI cycle that is relevant in the context of their unit's current status. We will also work to simultaneously identify facilitators and barriers to QI project implementation at the institutional level by conducting focus groups, surveys, site visits and discussions with front-line staff and families at units to pinpoint items that may impact QI implementation.

Cluster 2: Association of maternal, perinatal, and neonatal care with outcomes

Despite a lack of data from large multicenter studies, several emerging and established maternal, perinatal, and neonatal practices are variably implemented in PTB care centers across Canada. In Cluster 2, we will identify variable practices, and assess and associate the variability to neonatal outcomes. Some of the planned initiatives are described below.

1. *Deferred cord clamping and outcomes:* The practice of deferred cord clamping (DCC) is markedly variable in Canada (30-40% of preterm infants receive DCC).(22) We will collect information about DCC duration and reasons for immediate cord clamping, if DCC was not done. We will calculate the rate of change in DCC implementation over the three year study period and link data about DCC with neonatal outcomes.
2. *Antenatal steroids and neurodevelopmental outcomes:* Optimal administration of prenatal steroids to women at high risk of PTB can improve survival free of major morbidity in preterm infants.(23;24) However, there are concerns regarding adverse effects of steroids on the developing brain.(25) We will determine if optimal administration of antenatal steroids is associated with improved neurodevelopmental (ND) outcomes for neonates.
3. *Maternal antibiotic use and ND outcomes:* Mothers share their microbes with their infant and alteration of the early infant gut microbiome is correlated with the development of

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childhood obesity, asthma, allergies and diabetes (Type 1).(26-28) We will collect data on the intrapartum use of antibiotics by women with preterm premature rupture of membranes, spontaneous PTB, and following preterm labor and study the association between perinatal use of antibiotics and neonatal and ND outcomes.

4. *Preterm birth phenotypes and outcomes:* Some evidence suggests that PTB is a syndrome attributable to multiple pathologic processes(29;30) and that neonatal outcomes could be different based on the reasons for PTB. We will collect data on 6 categories of PTB: (a) preterm premature rupture of membranes, (b) infection, (c) hemorrhage, (d) hypertensive disorders of pregnancy, (e) other forms of medically indicated PTB, (f) multiple births, and (g) idiopathic PTB and attempt to link these to ND outcomes.
5. *Illness severity and ND outcome*: The management of threatened preterm labor has improved along with neonatal practices in the first golden hour(31) with gentler handling of neonates; however, the impact on illness severity and ND outcome is unknown. The PTB network will collect data regarding peripartum management strategies (*i.e.,* peripartum interventions, golden hour management) and correlate these with both neonatal illness severity on admission to the NICU (defined by Score of Neonatal Acute Physiology Perinatal Extension(32) and Transport Risk Index of Physiologic Stability(33)) and neonatal outcomes.
6. *Probiotics and ND outcomes:* Evidence suggests that probiotic administration to preterm neonates may reduce necrotizing enterocolitis(34) and nosocomial infection,(35) yet only 30% of Canadian neonates receive probiotics(22) We will attempt to link receipt of probiotics during the NICU stay, as well as type, form (powder vs. liquid), duration, and timing of probiotics use, with neonatal outcomes.

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7. *Respiratory management of preterm neonates and outcomes:* The need for and duration of invasive respiratory support after PTB is associated with bronchopulmonary dysplasia and other complications. However, the impact of different types of respiratory support and thresholds for different non-invasive, positive end-expiratory pressure (PEEP) on resource utilization and ND outcomes is unknown.(37-39) We will compare two protocols for the provision of respiratory support prior to intubation and after first extubation in preterm neonates using integrated comparative effectiveness research methods.
8. *Family-Integrated Care to improve outcomes:* Integration of families in the care of preterm neonates, particularly early parental engagement, early skin-to-skin care, and parent education, may improve outcomes of preterm neonates.(7) However, the minimal "dose" of these interventions is unknown. In a subset of NICUs, the PTB Network will evaluate the number of hours of 1) parent involvement, 2) skin-to-skin care, and 3) parent education and subsequent positive neonatal and ND outcomes.
9. *Sustainability of QI:* Sustainability of QI initiatives is an increasing concern for funders and stakeholders. The PTB Network will use standard methodology to evaluate QI initiatives in perinatology/neonatology for sustainability.

Cluster 3: Economics, resource utilization, and surveillance of PTB

Current cost estimation methods hint at the large economic burden of PTB in Canada, but they exclude maternal data, rely on simulation modelling, use crude provincial resource utilization data, and lack both granularity and inclusivity over time and across different subgroups.(40)

1. *Developing a costing algorithm for PTB in Canada:* We will develop a costing algorithm for PTB in Canada using a combination of prospective and retrospective data on patient-

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level resource utilization and resource-specific unit costs attained by purposive and representative sampling in Canada. We will collect resource utilization data from perinatal to post-neonatal periods for hospitalized infants from resources like CNN and the Discharge Abstract Database of the Canadian Institute of Health Information (CIHI). Unit costs will be calculated using billing data or through attributable costing methods. Using these data, we will generate a comprehensive algorithm compatible with data analysis programs.

2. *Estimating the economic burden of PTB in Canada:* The cost algorithm will be used to identify the economic burden on the healthcare system of both the entirety of PTB care and components of PTB care and to analyze how the costs vary by subpopulations, and provinces/territories in Canada. We will use retrospective and prospective nested cohort studies to assess healthcare costs accrued by the infant and the parents in the first 2 years after birth.
3. *Cost effectiveness of PTB interventions:* We will develop a system-wide economic decision model. The model will simulate hypothetical dyads of mothers/babies and will follow the dyad throughout the ante-, peri- and postnatal continuum. Data on resource utilization, unit costs, and health outcomes from the PTB Network, the Institute for Clinical Evaluative Sciences and other Canadian organizations, systematic reviews, and expert consultations will all be utilized in our model. This will allow us to estimate the cost-effectiveness of PTB interventions and identify those that offer the best outcomes and are economically efficient.
4. *Contemporary trends in Canadian PTB rates:* PTB surveillance in Canada lacks timely and accurate information on PTB rates. The most recent estimate for the PTB rate from

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the live birth files of Statistics Canada is 7.7% in 2010 and this figure excludes Ontario births.(1) The PTB Network will calculate both PTB rates and medically-indicated PTB rates (to identify system issues) in each provinces/territories using Canadian birth cohorts from 2017 to 2021 (supplemented with data from the 2003-2016 birth cohorts) from the Discharge Abstract Database of the CIHI and the MED-ECHO database in Quebec.

5. *Resource utilization by preterm infants:* The number of moderately and late preterm infants (32-36 weeks) has risen in recent years creating a need to identify which medical resources these preterm infants use and predictors of increased resource use. We will identify the health resource utilization patterns during hospitalization and after discharge for preterm infants in the first 2 years after birth.
6. *Evaluation of parental experiences:* Integration of families into the care of preterm infants is important to achieve the best neonatal outcomes(7), but feedback regarding parent satisfaction with care and suggestions for improvement is not routinely collected. In addition, the experience of the child and parent post-discharge is not regularly communicated back to the NICU or Neonatal Follow-up programs. We will develop an electronic web-based platform to capture parental experiences with the medical system during their child's hospitalization and for 2 years post-NICU discharge.

Ethics, data analysis, and timeline

Data coordination and ethics

The coordination center for the PTB Network will be located at the Maternal-Infant Care Research Center at Mount Sinai Hospital, Toronto. The centralized data management system conforms to both the Health Information Protection Act and Privacy and Personal Information

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Protection Act regulations and is approved by the Mount Sinai research ethics board for collection, development, and hosting of the PTB Network dataset, in order to ensure data integrity and security. Individual sites will receive approval from local research ethics boards, or quality improvement committees as appropriate.

Sample size

During the 3 years of data collection, we will prospectively collect information on ~1500 infants <29 weeks' gestation per year. Assuming 15% mortality and 20% loss to follow-up, we anticipate we will collect neonatal and ND outcome data from 1000 neonates per year. A sample this size will provide >90% power to detect a 30% relative increase in survival free of neonatal morbidity (baseline 47% to 61%) and 30% relative decrease in significant ND impairment (baseline 17% to 11.9%) in the last year compared with the first year at a significance level of 0.05 after accounting for clustering within each site.(41) Under the same assumptions, a conservative estimate of 20% change in the two outcomes will have >80% power. Sample size for nested cohorts will be determined based on feasibility.

Analyses plan

We plan to utilize specific QI based analyses to identify special-cause variation, adjusted analyses to generate standardize ratios, and comparative plots for site comparisons. Analysis details are provided in Appendix 1.

Timeline

The research described in this PTB Network protocol will continue through 2021. Nested cohort studies of economic, parental experiences, and specific projects will be spread over the study duration as outlined in Figure 2.

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Interpretation

PTB is expensive and not uncommon. Every year, 25 000 to 30 000 preterm infants are born in Canada(42) and the majority survive for >70 years, impacting the healthcare system to a greater extent than any other chronic condition. Thus, improving PTB outcomes can significantly improve quality of life and reduce healthcare costs over the life-course. In this program, we propose to address existing gaps in maternal-perinatal-neonatal research and strive for outcomes improvement by creating a transdisciplinary team working within an objectively-structured performance measurement framework.

Conclusion

The PTB Network will be a national network encompassing the spectrum of maternal-fetal-neonatal-childhood events that affect outcomes of preterm infants. Our goals for the PTB Network are three fold: 1) to enable multidisciplinary evidence-based practice change that results in improved neonatal outcomes, 2) to evaluate and standardize PTB interventions across Canada by associating practices with improved outcomes, and 3) to estimate the economic burden of PTB and the cost-effectiveness of PTB interventions with the objective of improving the standard of care and guiding efficient resource allocation.

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Authors' contributions

All investigators conceived of the PTB Network concept, PSS led the protocol design process, and drafted the manuscript. All the remaining authors (SDM, JB, AS, KR, JF, JCP, KSJ, BP, TL, KO, SS, NC, PP) participated in network and protocol design, and will direct the collection of data, dissemination of knowledge, and implementation of practice changes. All authors approved the final manuscript.

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Figure legends

Figure 1: Map of the Canadian Preterm Birth Network

Red dots indicate approximate location of all 31 participating hospitals.

Abbreviations: CNN, Canadian Neonatal Network; CNFUN, Canadian Neonatal Follow-Up Network; CAPSNet, Canadian Pediatric Surgery Network; CSMFM, Canadian Society of Maternal Fetal Medicine

Figure 2: Timeline of PTB Network research projects

Depiction of the approximate timeline for projects described in the PTB Network Clusters.

*Projects not described in this protocol

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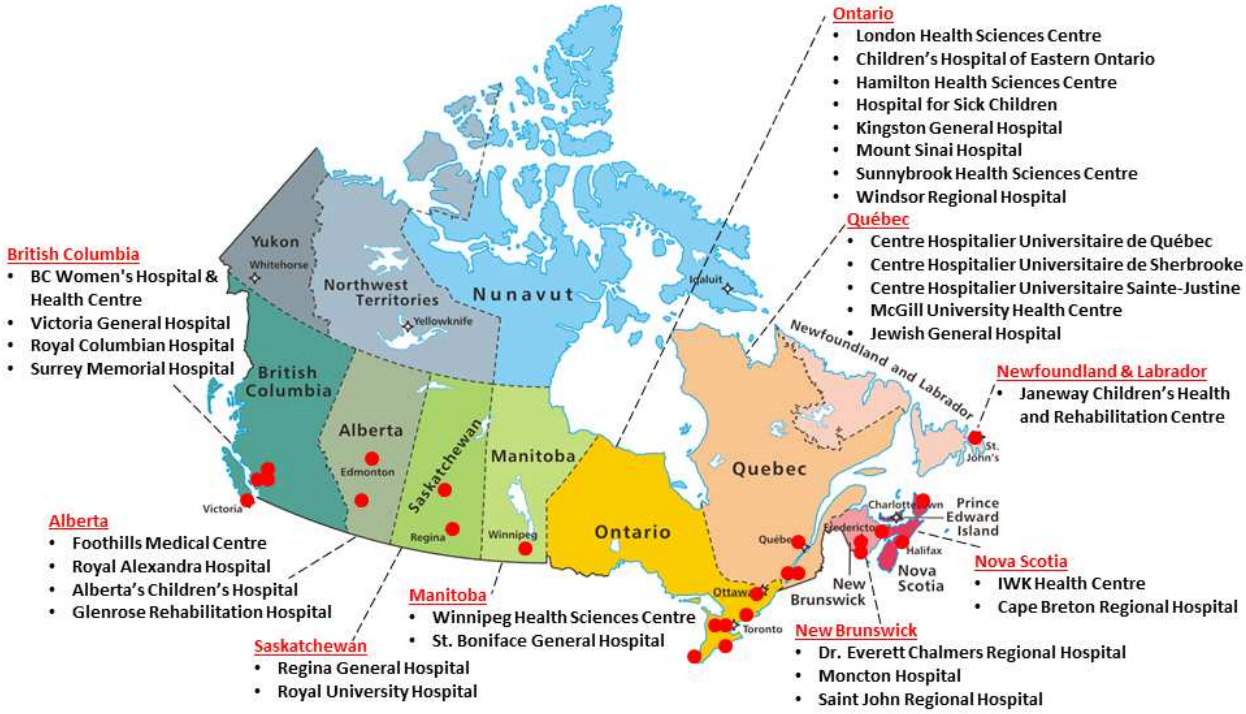
Canadian Preterm Birth Network

CNN – CNFUN – CNTN – CAPSNet – CSMFM



British Columbia
- BC Women's Hospital & Health Centre
- Victoria General Hospital
- Royal Columbian Hospital
- Surrey Memorial Hospital

Alberta
- Foothills Medical Centre
- Royal Alexandra Hospital
- Alberta's Children's Hospital
- Glenrose Rehabilitation Hospital

Saskatchewan
- Regina General Hospital
- Royal University Hospital

Manitoba
- Winnipeg Health Sciences Centre
- St. Boniface General Hospital

Ontario
- London Health Sciences Centre
- Children's Hospital of Eastern Ontario
- Hamilton Health Sciences Centre
- Hospital for Sick Children
- Kingston General Hospital
- Mount Sinai Hospital
- Sunnybrook Health Sciences Centre
- Windsor Regional Hospital

Québec
- Centre Hospitalier Universitaire de Québec
- Centre Hospitalier Universitaire de Sherbrooke
- Centre Hospitalier Universitaire Sainte-Justine
- McGill University Health Centre
- Jewish General Hospital

Newfoundland & Labrador
- Janeway Children's Health and Rehabilitation Centre

Nova Scotia
- IWK Health Centre
- Cape Breton Regional Hospital

New Brunswick
- Dr. Everett Chalmers Regional Hospital
- Moncton Hospital
- Saint John Regional Hospital

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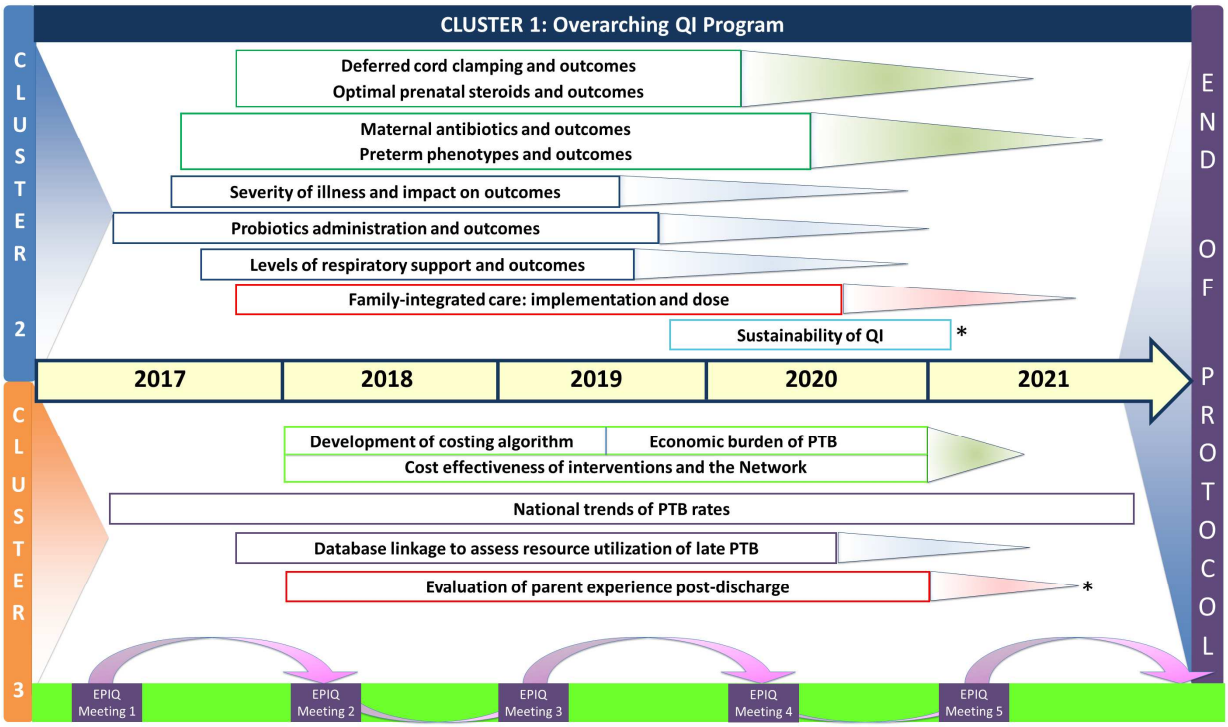

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Appendix 1

QI analyses

To track the impact of all QI initiatives we will monitor sites' progress by analyzing the common cause and special cause variations of process measures using upper and lower control limits (UCL and LCL) in a Shewhart chart (control chart or P chart) every three months and identifying positive changes.(21;43) When special cause variation is not identified, sites will assume that the process is "stable" and sites will implement the next QI strategy. In the event of a practice change with the potential for unintended consequences, the team will use the lower control limit (2 sigma, rather than 3 sigma) to abandon the practice. Sites' progress will also be analyzed using benchmarking. For each outcome, we will calculate adjusted rates and associated 95% confidence intervals and present them graphically using caterpillar plots to visually differentiate between EPIQ sites. We will use indirect standardization to estimate standardized ratios and adjust for multiple baseline characteristics and differences in important health care practices. The expected number of events will be computed as the sum of predicted probabilities from a Bayesian hierarchical generalized linear model (multilevel logistic regression or zero inflated negative binomial models, depending upon data distribution) of all individual patient data from all participating sites adjusted for patient and hospital level attributes. The Bayesian model will also allow us to stabilize the rate for small hospitals with few admissions. We will graphically display site standardized ratios using funnel plots with 95% prediction intervals to examine the variation between sites within the PTB Network.

Comparisons and trends analysis

The PTB Network will collect data from the baseline year, 2018, until the last intervention year, 2020. We will compare infant characteristics over years, using a Chi-square test, ANOVA or

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Wilcoxon Rank Sum test, as appropriate. To test trends in infant characteristics; temporal trends; and variations in PTB rates, phenotypes, and subtypes (e.g., late, moderate, and extreme PTB; spontaneous and medically-indicated PTB) in Canada we will use a Cochran-Armitage trend test or linear regression as applicable. Overall outcomes will be compared using the Cochran-Mantel-Haenszel test to account for clustering within each site and Bayesian hierarchical generalized linear models adjusting for confounders, risk factors, and site characteristics. If applicable, we will perform piecewise hierarchical linear (over time) regression modeling with autoregressive covariance structure and a time series approach, adjusting for patient and site level factors, to assess the effectiveness of the interventions. Sub-analysis stratified by GA (< 26 weeks' and 26 – 29 weeks' GA groups) will be conducted.

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Appendix 2

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The Canadian Preterm Birth Network: a study protocol for improving outcomes for preterm infants and their families

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Found on p.1 in title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Found on p. 3 in abstract
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Found on p. 4 in introduction
Objectives	3	State specific objectives, including any prespecified hypotheses Found on p. 4-5 in introduction
Methods		
Study design	4	Present key elements of study design early in the paper Found on p. 5-6 in methods, p. 6-9 in sections Cluster 1, cluster 2 and cluster 3.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Found on p. 5-6 in methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Found on p. 5-6 in methods *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable paper Found on p. 5-6 in methods, p. 6-9 in sections Cluster 1, cluster 2 and cluster 3.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Found on p. 5-6 in methods; p. 11-12 in ethics, data collection, and timeline; and appendix 1.
Bias	9	Describe any efforts to address potential sources of bias Found in appendix 1
Study size	10	Explain how the study size was arrived at Found on p. 5-6 in methods, study population
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Found in appendix 1, TBD
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Found in appendix 1, TBD
		(*b*) Describe any methods used to examine subgroups and interactions Found in

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		appendix 1, TBD
		(*c*) Explain how missing data were addressed Found in appendix 1, TBD
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressedTBD *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants TBD	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data TBD	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data TBD	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results TBD	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses TBD	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives Found on p.13Interpretation and conclusion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias TBD
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence TBD
Generalisability	21	Discuss the generalisability (external validity) of the study results objectives Found on p.13Interpretation and conclusion
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Found on p.2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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