**Title:** Redefining the significance and treatment threshold of patent ductus arteriosus among preterm neonates (RESET-PDA)

**Proposed amendment:**

To collect, as part of Canadian Neonatal Network (CNN), additional data fields for preterm infants who are diagnosed with hemodynamically significant patent ductus arteriosus in tertiary NICUs across Canada.

The CNN coordinating centre and the participating sites will follow the same protocol for the core CNN database. The database expansion for the RESET-PDA study is described in this amendment.

**Duration:** Three years [projected dates 1st October 2021 to 30th September 2024].

**Background/Rationale:**

**Patent ductus arteriosus and adverse outcomes among extremely preterm infants**

Patent ductus arteriosus (PDA) is the most common congenital heart defect among preterm neonates and may be a significant cause of mortality and morbidity.[[1](#_ENREF_1)] PDA occurs in approximately 65% of extremely preterm neonates (defined as gestational age [GA] ≤ 27+6 weeks), affecting 850 neonates across Canada annually.[[2](#_ENREF_2)] PDA results in a vascular shunt from the aorta to the pulmonary artery and its effects include lung edema and prolonged ventilator and oxygen dependency,[[3](#_ENREF_3)] and systemic hypoperfusion as blood is diverted away from the systemic circulation and myocardium[[4](#_ENREF_4)] to the lungs. PDA is associated with increased mortality, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and intracranial hemorrhage (ICH) (Table 1).[[5-7](#_ENREF_5)] Furthermore, increased duration of exposure to PDA is associated with increased mortality and morbidity.[[8](#_ENREF_8)] Management options for PDA include cyclooxygenase inhibitors (e.g. ibuprofen) or surgical or device closure, and/or therapies to mitigate the effects of a PDA (e.g. diuretics).[[9](#_ENREF_9)]

**Lack of consensus about the definition of ‘significant’ PDA**

Despite over four decades and 60 randomized clinical trials, neonatologists remain uncertain about “which PDA should be treated?” Trials of various approaches to PDA treatment have demonstrated that pharmacotherapy facilitates earlier ductal closure but does not improve neonatal and neurodevelopmental outcomes However, limitations in study design restrict their external validity to contemporary management of ELGANs with PDA. A significant knowledge gaps in clinical management is a lack of understanding of which PDAs are ‘hemodynamically significant’, a description which refers to the attempt to objectively appraise the magnitude of the ductal shunt and discriminate which PDAs may be causally linked to increased need for intensive care support and adverse outcomes.[[10](#_ENREF_10)] While preterm neonates with small PDA (ductal diameter ≤ 1.4mm) are broadly considered to not merit treatment[[11](#_ENREF_11)] owing to low shunt volume, early spontaneous resolution[[12](#_ENREF_12)] and no association with adverse outcomes,[[6](#_ENREF_6)] there is no consensus regarding any other clinical and/or echocardiography characteristics. While clinical trials of treatment of infants with ‘moderate or large’ PDA have not demonstrated improvement in neonatal or neurodevelopmental outcomes, no study has validated PDA disease severity against clinical outcomes. [[13-17](#_ENREF_13)] This knowledge gap creates doubt regarding the relevance of past studies to contemporary practice, which probably contributes to the ongoing ubiquitous clinical administration of treatment aimed at facilitating PDA closure (cyclooxygenase inhibitors, acetaminophen, and surgical/device closure) in Canada despite lack of proven benefit. Prediction models that accurately identify which preterm neonates with PDA are at risk for mortality and morbidity are urgently needed to inform clinical practice and select patients for future clinical trials aimed at modulating its negative short- and long-term impact.

**Defining ‘significant PDA’ is a priority because the smallest ELGANs are at increased risk of adverse outcomes when PDA treatment is avoided**

Despite their limitations, lack of improvement in neonatal outcomes in clinical trials of PDA treatment has, over the past decade, shifted the landscape of PDA management toward more selective treatment.[[18](#_ENREF_18),[19](#_ENREF_19)] However, it remains unclear which ELGANs to select for treatment and there is concern regarding the potential adverse effects of indiscriminate avoidance of PDA treatment.[[20](#_ENREF_20)] Observational studies have associated decreased pharmacological and surgical treatment with increased morbidity among the smallest and highest-risk ELGANs.[[21](#_ENREF_21)] In a multicentre study of repeated measures aggregated data from NICUs in the California Perinatal Quality Care Initiative, dose-response associations were identified between annual reductions in NICU-specific PDA treatment and increased rates of all-cause mortality among the smallest ELGANs. Each percentage point decrease in pharmacological treatment or surgical ligation was associated with a 0.21% (95% CI 0.06-0.35, p<0.01) increase in mortality among infants with birthweight 400-749g.[[22](#_ENREF_22)] In contrast, more mature preterm infants have experienced lower or unchanged morbidity associated with reduced PDA treatment.[[22](#_ENREF_22)] The divergence in outcomes associated with reductions in PDA treatment (higher mortality among the smallest and most immature infants but reduced morbidity among more mature infants) underscores the importance of identifying which ELGANs with PDA are at risk.

**Methods:**

**Project Objective:** To extend Canadian Neonatal Network data collection to include additional clinical and echocardiography data for extremely preterm neonates with PDA to develop an outcome-based definition of ‘significant’ PDA among extremely preterm neonates.

**Inclusion Criteria:** All neonates < 28 weeks GA diagnosed with patent ductus arteriosus (diameter ≥ 1.5mm)

**Exclusion Criteria:** 1. Congenital cardiac anomalies except patent ductus arteriosus, patent foramen ovale or ventricular septal defect. 2. Known genetic anomaly

**Main Outcome:** Death before hospital discharge OR moderate-severe neonatal morbidity, defined as ≥1 of (A) moderate-severe BPD (National Institute of Child Health and Human Development consensus definition: oxygen or positive pressure support at 36 weeks corrected GA);[[23](#_ENREF_23)] (B) moderate-severe NEC (Bell’s stage ≥ 2a)[[24](#_ENREF_24)]; or (C) severe intracranial hemorrhage (ICH)[[25](#_ENREF_25)] (large intraventricular hemorrhage (IVH) with dilatation,[[26](#_ENREF_26)] periventricular venous hemorrhagic infarction and/or severe post-hemorrhagic ventricular dilatation). This composite outcome was selected to include mortality and PDA-related neonatal morbidities, which may be competing outcomes.

**Study Design and Implementation:** To minimize the costs of database development, and reduce the duplication of effort on data collection we plan on integrating the RESET-PDA data collection using the pre-existing Canadian Neonatal Network data infrastructure. The clinical and echocardiography PDA variables will be added to the CNN database as an additional page which will be enabled only for the RESET-PDA study personnel at each site with designated login. The proposed additional data fields do not contain any identifying information. The new page will be tested and validated by the CNN database developer. By linking this PDA data to the existing CNN database, we will be able to link our data to clinical outcomes data already collected by the Canadian Neonatal Network. Only qualified TnECHO clinicians or delegates supervised by them, and not regular data abstractors, at each site will be responsible for collecting the additional data as outlined in this amendment, as this requires oversight by individuals with specific clinical expertise (Data collection form attached – items will be incorporated to the CNN database as a separate page for the RESET-PDA study). Participating sites will retrospectively abstract collected data. Study data will be uploaded to the CNN database via the current secure CNN system and are governed by the data sharing agreements that are in place between the coordinating centre at Mount Sinai Hospital and the participating sites.

**Proposed Data Collection:** We propose a 3-year period of augmenting the CNN data collection for participating centres with comprehensive clinical and echocardiography data of PDA evaluation and treatment.

**Model Development and Statistical Analysis:** Four distinct, clinically relevant, and pragmatic postnatal age specific prediction models will be developed using the main study outcome, based on age of PDA evaluation after birth: (1) 1-3 days, (2) 4-7 days, (3) 8-14 days and (4) 15-28 days. Postnatal-age specific models provide a more homogeneous population for modelling and may be more applicable to clinical practice. For each model, detailed clinical and imaging data (see below) from echocardiography evaluations which identify a PDA and occur in the respective timeframe will be abstracted and included in the model. Among infants with more than one echocardiogram during each designated timeframe, the first echocardiogram will be used to avoid bias owing to differences in the number of echocardiograms performed. Data from the same infant may be incorporated into more than one postnatal age specific model. Importantly, because most ICH occurs prior to 4 days of age,[[27](#_ENREF_27)] the composite outcome for the later three prediction models (4-7 days, 8-14 days, 15-28 days) will comprise death/ moderate-severe BPD/ moderate-severe NEC but omit severe ICH. Model derivation will be performed using the first two years of study participants (derivation cohort). Internal validation of the model will be conducted in the complete derivation cohort using the bootstrap method . The study participants enrolled during the third year of the study will be used as the test data set for external validation.

***Clinical measures-predictor variable data:***

Model development will include clinical variables to control for confounding within our models for mortality, severe ICH, moderate-severe BPD and NEC [Figure 1]. Baseline perinatal data will comprise patient demographics (GA, birthweight z-score for GA, multiple gestation, outborn, and **sex** [an established independent predictor of mortality and BPD][[28](#_ENREF_28),[29](#_ENREF_29)]), perinatal risk factors (maternal corticosteroid exposure, pre-eclampsia, clinical chorioamnionitis, delivery mode), and prognostic early postnatal measures of illness severity estimated in the first 24 hours of life, such as mechanical ventilation,[[30](#_ENREF_30)] inotropic support,[[31](#_ENREF_31)] surfactant administration,[[32](#_ENREF_32)] and the Score for Neonatal Acute Physiology II which is a validated predictor of mortality,[[33](#_ENREF_33),[34](#_ENREF_34)] and BPD.[[35](#_ENREF_35)] Time-varying postnatal characteristics associated with neonatal morbidity, such as duration and intensity of mechanical ventilation and sepsis, will be incorporated in model development for the days of life prior to the echocardiogram. CNN routinely abstracts the mode of respiratory support (e.g. high frequency ventilation) for each day after birth. Each ELGAN’s blood pressure, mean airway pressure (MAP), peripheral capillary oxygen saturation (SpO2), and fraction of inspired oxygen (FiO2) will be abstracted to characterize the respiratory support at a steady state just prior to the echocardiogram. We will incorporate the oxygen saturation index (MAP x FiO2 x 100 / SpO2), which has been validated as a reliable, non-invasive alternative to the oxygenation index for assessing neonatal hypoxic respiratory failure.[[36](#_ENREF_36),[37](#_ENREF_37)] Model development will also account for centre-level characteristics (clustering) such as use of routine echocardiography screening (vs. for clinical symptoms) and propensity to administer pharmacological and/or surgical treatment.

***Echocardiography predictors***

Imaging methods will be in-line with previous publications and guidelines on comprehensive 2D-echocardiography in neonates. A standardized echocardiography protocol, including methodology for measurement of echocardiography parameters, has been adopted by all study sites. Echocardiography parameters that will be considered as potential covariates in the models include those representing PDA size and flow pattern, left heart volume loading and function, right heart pressure and function, ventricular-arterial coupling, and alterations in systemic arterial diastolic flow[[38](#_ENREF_38)] (Appendix). These parameters have been selected due to their previously demonstrated association with PDA as markers of ductal shunt volume,[[39](#_ENREF_39)] and demonstrated low inter- and intra-rater variability in neonatal[[40-42](#_ENREF_40)] and paediatric[[43](#_ENREF_43)] populations. While some proposed echocardiography parameters have been reported to have suboptimal reliability (e.g. LA:Ao ratio), these are measures that are widely used in clinical practice and will therefore be collected and evaluated as a potential covariate in the prediction models.

***Descriptive and univariate analyses***

To identify the potential covariates for model development, clinical and echocardiography characteristics will be compared between ELGANs with PDA who survive without morbidity vs. those who die or develop moderate-severe morbidity, using the Pearson χ2 test for categorical covariates and the Student t-test or Wilcoxon Rank-Sum test for continuous covariates.

***Partial least square discriminate analysis (PLS-DA)***

A generalized logistic regression model will be developed to predict the primary composite outcome. Due to the potential for correlated variables in this study, especially among the many related echocardiography parameters, partial least square discriminate analysis (PLS-DA) will be used as a dimension-reduction tool.[[44](#_ENREF_44)] First, for dimension-reduction, we will conduct PLS-DA analysis for the potential predictors identified in the univariate analyses, the receipt of prior pharmacological PDA treatment and its interaction with potential predictors (denoted as X = [x1, x2, …, xm]), and the primary outcome (denoted as Y). A set of *p* PLS principal components u1, u2, …, up (where *p* is necessarily less than *m*) will be created, where u1,u2,…,up are uncorrelated latent variables and linear combinations of the original potential predictors for the primary outcome. Second, multivariate logistic regression analysis will be performed using the identified PLS components as covariates and the primary outcome as the dependent variable, with generalized estimating equations to account for clustering within each site (‘centre effects’) and multiples (e.g., twins). The number of PLS principal components to be retained for the final model will be determined using a forward stepwise selection procedure (principal components retained if p<0.10).

***Model calibration, performance, and validation***

Measures of predictive accuracy will be evaluated considering the highest probability estimate as the predicted outcome and a range of cut-off points. Model fit will be evaluated using the Hosmer and Lemeshow Goodness-of-Fit Test (p>0.05).[[45](#_ENREF_45)] Nagelkerke-R2 will be used to determine overall performance. The calibration slope will be used to evaluate the agreement between the observed and predicted risk of the primary outcome. The c-statistic of the final model will be used to evaluate model discrimination and will be presented as AUC with 95% CI. Internal validation will be performed using a bootstrap optimism correction computed based on 200 random bootstrap samples with replacement from the complete derivation cohort.[[46](#_ENREF_46)] For each bootstrap sample, PLS-DA will be performed and the AUC determined. The optimism correction will be computed as the difference in AUC between the original model and the bootstrap model. The overall bootstrap optimism correction will be computed as the mean of all optimism corrections. The bootstrap corrected AUC will be estimated by subtracting the overall bootstrap optimism correction from the AUC from the final PLS-DA model developed using the original complete derivation dataset/cohort. We will further conduct external validation in the test dataset by examining the performance of the developed models using the calibration slope and the c-statistic/AUC.[[47](#_ENREF_47)]

***Defining ‘significant PDA’ (sPDA)***

The clinical and echocardiography covariates retained in the PLS-DA model that best predict the primary outcome will then be used to define sPDA. To be specific, let x1,..,xp be the covariates retained in the predictive model: logit (prob(outcome=1|x1,..,xp)) = a0+ a1∙x1+ a2∙x2 +…+ ak∙xk, we will define a PDA severity-score (PDAsc) as PDAsc = a1∙x1 + a2∙x2 +…+ ak∙xk. A cut-off, u, that maximizes Youden’s index[[48](#_ENREF_48)] will then be used to define sPDA = (PDAsc>u). Maximizing Youden’s index is an appropriate method in our study given the importance of incorporating both the risks and benefits of *overtreatment* and *undertreatment* of PDA.[[49-51](#_ENREF_49)]

***Sample Size***

Sample size justification is based on the requirement for developing the predictive models for the primary outcome, for which approximately 15 independent covariates are anticipated. The event rate of the primary outcome is 50%[[2](#_ENREF_2)]. Based on a conservative 20:1 event-to-variable ratio,[[52](#_ENREF_52)] about 600 ELGANs with PDA would be required for the derivation sample of each model (15 variables x 20 events per variable / 50% event rate) and an additional 250 ELGANs to form the test cohort for external validation [total of 850 ELGANs for the combined derivation and external validation samples for each model]. Based on recent CNN data and a national survey conducted to inform this project, we estimate that over a 3-year recruitment period, approximately 840, 1038, and 522 ELGANs are first diagnosed with PDA on echocardiogram during the Day 1-3, 4-7 and 8-14 postnatal periods, respectively. Further, as the above numbers of ELGANs represent the timing of the *first* echocardiogram and based on an average of 2.5 scans per ELGAN in the first month, it is estimated that the Day 8-14 and 15-28 models will each incorporate 900-1100 eligible echocardiograms. Therefore, the 3-year period of enrolment will enable recruitment to power model development and validation for all models in this study.

**Potential Harms:**There are no specific harms that may be caused in the amendment of the CNN database. As with any data collection repository, there is the risk of a breach of privacy and confidentiality, though this risk is not materially increased with the abstraction of additional data fields for this study. This risk will be minimized by taking the precautions with respect to data storage, retention, and destruction.

**Potential Benefits:**There are no potential benefits for individual subjects. The benefit of this database is the potential for knowledge generation which may result in standardized and improved treatment and outcomes in future for this group of patients.

**Governance of RESET-PDA data**: Each participating site will retain ownership of the data for their patients contained in the database and will have obtained REB approval permitting the use of the data.

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# APPENDIX

## Table: List of Echocardiography Parameters

|  |  |  |
| --- | --- | --- |
| **Left ventricular (LV) parameters** | **Right ventricular (RV) parameters** | **Pulmonary hemodynamics** |
| **Dimensions:**  LV end diastolic volume (LVEDV)  LV end systolic volume (LVESV)  LV internal diameter in diastole (LVIDd)  LV internal diameter in systole (LVIDs) | **Dimensions**  RV end diastolic area (RVEDA)  RV end systolic area (RVESA)  RV internal diameter in diastole (RVIDd) | Pulmonary artery acceleration time (PAAT)  RV ejection time (RVET)  Sphericity/Eccentricity index |
| **Systolic Function**  Tissue Doppler Imaging (s') | **Systolic Function**  Tricuspid Annular Plane Systolic Excursion  Tissue Doppler Imaging (s') | **Vascular and PDA parameters**  PDA diameter  Max and mean pressure gradient  Shunt direction  Abdominal aorta, celiac artery, and middle cerebral artery diastolic flow direction |
| **Diastolic Function**  Mitral valve inflow velocities (E) (A)  Tissue Doppler imaging (e') (a')  Isovolumic relaxation time (IVRT)  LV (E/e’)  Pulmonary vein inflow velocities (S) (D) |
| ***Additional calculations:***  LV stroke volume and output (LVO)  Fractional shortening (FS)  Ejection fraction (Simpson’s biplane)  Left atrium to aortic root ratio | ***Additional calculations:***  Fractional area change | **Other Parameters**  Aortic annulus diameter in peak systole |

## Clinical Data Collection Form

**Clinical data associated with each echocardiogram:**

Date of echocardiogram

Weight

Mode of ventilation at echo: High frequency ventilation (jet or oscillation) / conventional ventilation / nasal high-frequency oscillation / nasal intermittent positive pressure ventilation / nasal continuous positive airway pressure / heated and humidified high-flow nasal cannula / low flow oxygen /no support / other (specify)

Systolic, diastolic, and mean blood pressure

Median SpO2, mean airway pressure, fraction of inspired oxygen in the 6 hours prior to start of echocardiogram

**PDA treatment course commenced within 3 days of the echocardiogram:**

PDA pharmacological treatment commenced within 3 days of the echocardiogram: Yes / No

Date of first dose of treatment course

Medication administered:

Indomethacin / Ibuprofen / Acetaminophen / Co-administration of indomethacin + acetaminophen / Co-administration of ibuprofen + acetaminophen

Total dose administered (mg/kg)

Route of administration: Intravenous / Enteral / Rectal / Intravenous and Enteral (Combination)

Number of doses administered

If complete course not administered, primary reason for stopping early: death, NEC, sepsis, enteral intolerance, renal insufficiency, bleeding, PDA closure, other (specify)

**Other**

***Surgical PDA closure***

Type of surgery: Catheter Device Closure / Ligation

Date of surgery:

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