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Selective early medical treatment of the patent ductus arteriosus in extremely low gestational age infants: a pilot randomised controlled trial protocol (SMART-PDA)

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ABSTRACT

Introduction Patent ductus arteriosus (PDA) is the most common cardiovascular problem that develops in extremely preterm infants and is associated with poor clinical outcomes. Uncertainty exists on whether early pharmacotherapeutic treatment of a clinically symptomatic and echocardiography-confirmed haemodynamically significant PDA in extremely preterm infants improves outcomes. Given the wide variation in the approach to PDA treatment in this gestational age (GA) group, a randomised trial design is essential to address the question. Before embarking on a large RCT in this vulnerable population, it is important to establish the feasibility of such a trial.

Methods and analysis *Design:* a multi-centre, open-labelled, parallel-designed pilot randomised controlled trial.

Participants: preterm infants born <26 weeks of gestation with a PDA diagnosed within 72 hours after birth.

Intervention (selective early medical treatment (SMART) strategy): selective early pharmacological treatment of a moderate-severe PDA shunt (identified based on pre-defined clinical signs and routine screening echocardiography) within the first 72 postnatal hours with provision for repeat treatment if moderate-severe shunt persists.

Comparison (early conservative management strategy): no treatment of PDA in the first postnatal week.

Primary outcomes: (1) proportion of eligible infants recruited during the study period; (2) proportion of randomised infants treated outside of protocol-mandated therapy.

Sites and sample size: the study is being conducted in seven neonatal intensive care units across Canada and the USA with a target of 100 randomised infants.

Analysis: the primary feasibility outcomes will be expressed as proportions. A pre-planned Bayesian analysis will be conducted for secondary clinical outcomes such as mortality, severe intraventricular haemorrhage, procedural PDA closure and chronic lung disease to aid stakeholders including parent representatives decide on the appropriateness of enrolling this vulnerable population in a larger trial if the feasibility of recruitment in the pilot trial is established.

Ethics and dissemination The study has been approved by the IWK Research Ethics Board (#1027298) and six additional participating sites. On the completion of the study, results will be presented at national and international meetings, published in peer-reviewed journals and incorporated into existing systematic reviews.

Trial registration number NCT05011149 (WHO Trial Registration Data Set in Appendix A).

Protocol version Ver 7.2 (dated July 19, 2023).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This randomised trial exclusively enrols infants born less than 26 weeks of gestational age.
⇒ Unlike previous patent ductus arteriosus (PDA) trials, the SMART-PDA trial combines clinical and echocardiographic criteria to grade the severity of the PDA shunt to decide on the treatment in the intervention group rather than deciding based on the PDA size and shunt directionality only.
⇒ Given this is a pilot trial to assess the feasibility of recruitment, information obtained from this trial should not be used for clinical decision-making.
⇒ The trial uses ibuprofen as first-line pharmacotherapy and therefore is unable to assess the feasibility of recruitment in centres using indomethacin or acetaminophen as the first-line therapy for PDA.

BACKGROUND

Patent ductus arteriosus (PDA) is the most common cardiovascular problem that develops in infants born extremely preterm and is associated with poor neonatal outcomes such as death, necrotising enterocolitis (NEC) or chronic lung disease (CLD).[1–6]

Randomised controlled trials (RCTs) exploring pharmacotherapeutic treatments for PDA have demonstrated that non-steroidal anti-inflammatory agents (indomethacin and ibuprofen) and acetaminophen are effective in closing a PDA.[7 8] However, existing RCTs have not been able to demonstrate a reduction in PDA-related adverse outcomes.[7–9] Yet, an overwhelming majority of clinicians continue to treat PDAs early in the smallest preterm infants.[10]

Evidence from observational studies suggests that an approach of early echocardiography screening and treatment might be beneficial in extremely preterm infants. In a French national population-based cohort of 1513 preterm infants, screening echocardiography and PDA treatment before postnatal day 3 in extreme preterms was associated with lower rates of in-hospital mortality and pulmonary haemorrhage.[11] Similar results have been demonstrated in a recent study from Iowa that showed a 23% absolute reduction in the primary outcome of death or severe BPD (p=0.002) in the cohort of 22–24 week GA infants with early haemodynamic screening.[12] This approach of early screening and treatment, however, has not been evaluated through adequately powered trials in infants at the highest risk of adverse clinical outcomes, such as those born <26 weeks of GA.

On the contrary, a conservative approach in the first postnatal week would lead to less exposure to potentially harmful medications as well as less resource use (less echocardiographic assessment). A recent RCT on early ibuprofen therapy for PDA in extremely preterm infants born <28 weeks of GA (the Beneductus Trial) not only demonstrated the non-inferiority of an expectant management approach versus early pharmacotherapy but, in fact, the composite outcome of death/NEC/CLD was worse in the early treatment group (absolute risk difference −17.6%; 95% CI, −30.2 to −5.0).[13] It is not clear whether this reflects the elimination of an important role for the PDA in some patients or unanticipated harmful effects on the developing lung in those patients whose PDA was unresponsive to treatment. Therefore, an early conservative approach might be a safer option to manage PDA, especially in micropreemies at <26 weeks of GA, who are at a high risk of PDA-attributable morbidity as well as medication-related adverse effects.

Given the strong pathophysiological rationale of adopting either approach, there is always a risk of significant protocol violations while attempting to address this question through a large RCT. To our knowledge, no RCT on PDA management has ever been conducted that exclusively enrols micropreemies born at <26 weeks of GA. Two recent pilot RCTs on early PDA treatment within a similar timeframe (within 48 hours by El Khuffash *et al* from Ireland and within 72 hours by de Waal *et al* from Australia) have shown wide variation in recruitment rates (88% vs 54%, respectively).[14 15] Furthermore, another recent multi-centre RCT on early targeted treatment of the PDA conducted in France (TRIOCAPI trial) showed that open-labelled treatment occurred in 62.3% of infants at a median age of 4 days, which substantially dilutes the trial results and interpretation.[16] Therefore, a pilot trial to assess the feasibility of recruitment and protocol adherence is required before designing a large multi-centre trial.

Research question and objectives

The overall purpose of this pilot RCT is to assess the feasibility of conducting a large RCT to explore the following research question: *"In preterm infants born <26 weeks' GA, does a strategy of selective early treatment of a moderate-severe PDA shunt (based on pre-defined clinical and echocardiographic criteria) in the first postnatal week lead to reduction in the composite outcome of death or severe CLD when compared with an early conservative management strategy?"*

The study objectives are as follows:

1. The **primary objectives are to assess** (a) the proportion of eligible infants recruited in the trial and (b) the proportion of randomised infants with treatment outside of protocol-mandated therapy.
2. The **secondary objectives** are to (a) compare clinical outcomes between the planned comparison groups, (b) views of parents/guardians on enrollment in this RCT and (c) assess the feasibility of conducting a cost-effectiveness analysis for the main trial.

Primary hypothesis for the pilot RCT

Recruitment of preterm infants born at <26 weeks of GA in a trial of selective early medical treatment versus conservative management of the PDA is feasible with minimal protocol deviation.

METHODS

Study design

This is a multi-centre, open-labelled, parallel-designed pilot RCT. At the time of publication of this protocol, seven centres (four in Canada and three in the USA) have actively recruited in the trial. The protocol has been designed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) extension for randomised pilot and feasibility trials and the Standard Protocol Items: Recommendations for Interventional Trials guidance for reporting clinical trial protocols.[17–19] Recruitment for the study commenced on 10 January 2022, with a tentative completion date of September 2024.

Patient and public involvement in study design

A parent partner from the Canadian Premature Babies' Foundation, which is a parent-led, non-profit organisation providing education, support and advocacy for Canada's premature babies and their families, was involved in the design of the study including the development of eligibility criteria and prioritisation of outcome measures.

Eligibility criteria

Preterm infants born less than 26 completed weeks (ie, up to and including 25 weeks and 6 days) of gestation are eligible for enrolment following written informed

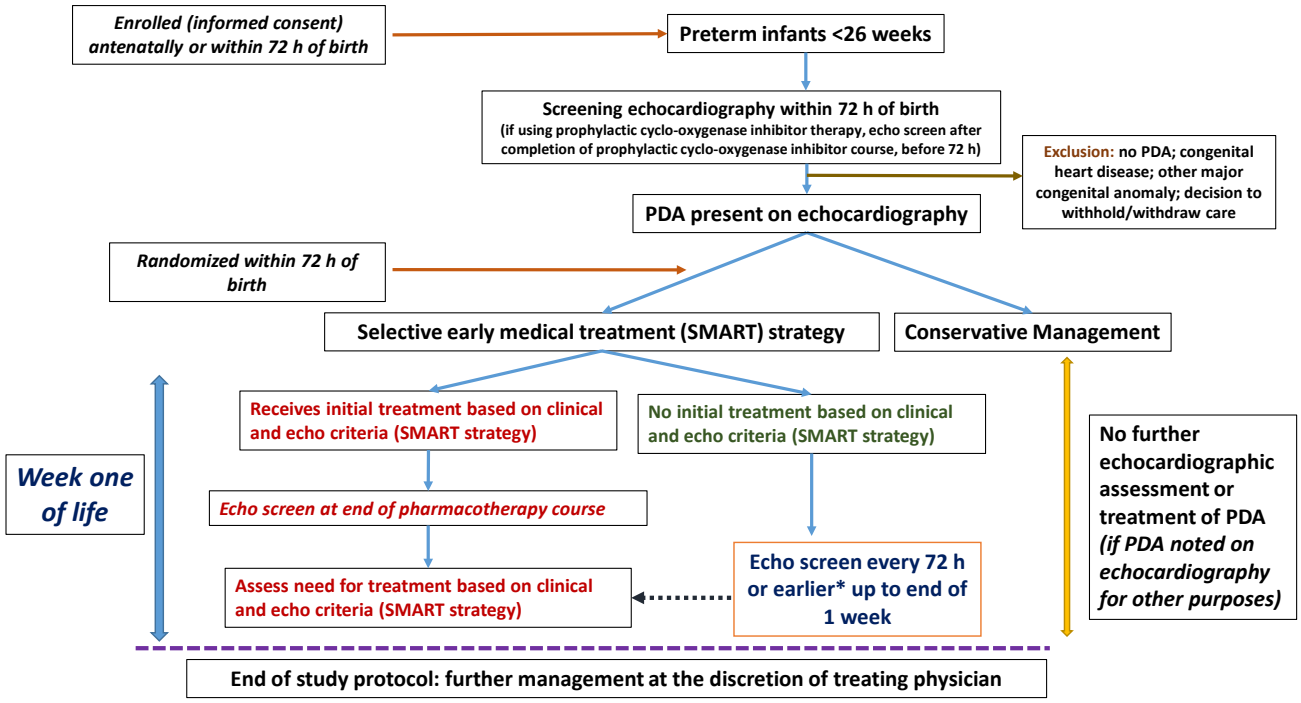

Figure 1 Study flow diagram. *If there is worsening clinical severity status. echo, echocardiography; PDA, patent ductus arteriosus.

consent from the parents/guardians antenatally or after birth (figure 1). All enrolled infants undergo a screening echocardiography within the first 72 hours of age. Infants with an open PDA (of any shunt severity) documented on the initial screening echocardiography, who do not satisfy any of the exclusion criteria described below, are potentially eligible for randomisation. Infants receiving prophylactic cyclo-oxygenase inhibitor therapy (indomethacin, ibuprofen or acetaminophen) are also eligible for inclusion if the screening echocardiography is performed after completion of the course of prophylactic cyclo-oxygenase inhibitor drug but before 72 hours of age.

Preterm infants born at <26 weeks of GA with an antenatally/postnatally diagnosed major congenital anomaly or congenital heart disease or infants where a decision has been made to withhold active management are not eligible for enrolment. Further, enrolled infants are not eligible for randomisation if (a) on initial screening echocardiography the PDA is closed or a major congenital heart disease is diagnosed (excluding patent foramen ovale, atrial septal defect or ventricular septal defect with a defect size of less than 2 mm) that precludes any PDA closure treatment or (b) a decision has been made to withdraw active management before randomisation.

Interventions

Experimental group (selective early medical treatment (SMART) strategy)

Infants randomised to the experimental group follow the SMART treatment protocol, which includes echocardiographic screening every 72 hours or earlier (if there is worsening clinical severity status) to categorise PDA disease severity by combining clinical and echocardiographic features (table 1). The PDA shunt severity is determined based on a combination of clinical and echocardiographic signs that have been adapted from validated classification systems and modified based on feedback from neonatologists practicing targeted neonatal echocardiography in Canada (table 1).[20–23] All echocardiographic assessments are done by physicians trained in targeted neonatal echocardiography (TNE) or by paediatric cardiologists (based on echocardiography protocols of participating sites). Details of the standardised echo views and measurements are outlined in online supplemental appendix B.

At any evaluation if patients are found to have a 'severe PDA' on echocardiography, irrespective of clinical symptoms, or a 'moderate PDA' on echocardiography with at least moderate clinical illness, they receive pharmacotherapy aimed at PDA closure. All other combinations are managed conservatively (ie, without the use of NSAIDs or acetaminophen) (table 2). Additionally, if the PDA shunt direction is not predominantly left-to-right (ie, ≤66% of the cardiac cycle), no treatment is immediately provided as PDA closure may be detrimental in the presence of pulmonary hypertension. However, the infant is screened with echocardiography every 72 hours (or earlier if there is worsening clinical severity status) as the PDA may become haemodynamically significant as pulmonary pressures decline over time.

Table 1 Clinical and echocardiographic measures of the haemodynamic significance of the patent ductus arteriosus (PDA)

Clinical signs (one or more)	Echocardiographic markers*
Mild: ► Need for supplemental oxygen (fraction of inspired oxygen (FiO_2)<30%) ► Need for non-invasive respiratory support or mechanical ventilation with mean airway pressure (MAP) <8 cm H_20	**Mild (A and one or more of B)** A. PDA size: <1.5 mm shunting predominantly left right (>66% of the cardiac cycle)† B. Pulmonary and systemic shunt effects 1. Left atrium: aortic root ratio <1.5 2. Transductal peak systolic velocity >2.0 m/s 3. Left ventricular output (ml/kg/min) <200 4. Diastolic flow pattern in the descending aorta: Normal antegrade flow
Moderate: ► Need for supplemental oxygen (FiO_2 requirement 30–50%) ► Need for non-invasive respiratory support or mechanical ventilation with mean airway pressure (MAP) 8–12 cm H_20 ► Oliguria (urine output <1 mL/kg/h) not explained by other clinical conditions (medications; birth asphyxia) ► Systemic hypotension (mean BP <gestational age in weeks at birth)	**Moderate (A and one or more of B)** A. PDA size: 1.5–2.5 mm shunting predominantly left right (>66% of the cardiac cycle)† B. Pulmonary and systemic shunt effects 1. Left atrium: aortic root ratio 1.5–2.0 2. Transductal peak systolic velocity 1.5–2.0 m/s 3. Left ventricular output (ml/kg/min) 200–400 4. Diastolic flow pattern in the descending aorta: Absent/retrograde
Severe: ► Need for supplemental oxygen (FiO_2 requirement>50%) ► Need for non-invasive respiratory support or mechanical ventilation with mean airway pressure (MAP) >12 cm H_20 ► Profound or recurrent pulmonary haemorrhage ► Acute renal failure (oliguria with elevated creatinine levels) ► Haemodynamic instability requiring >1 cardiotropic agent	**Severe (A and one or more of B)** A. PDA size: >2.5 mm shunting predominantly left right (>66% of the cardiac cycle)† B. Pulmonary and systemic shunt effects 1. Left atrium: aortic root ratio >2.0 2. Transductal peak systolic velocity <1.5 m/s 3. Left ventricular output (ml/kg/min) >400 4. Diastolic flow pattern in the descending aorta: Retrograde

*In the event that PDA size criteria do not match with any of the corresponding B criteria during a particular echocardiographic assessment (ie, all B criteria indicate a higher or lower degree of haemodynamic significance as compared with A criteria), the higher of the two will be used to assign the degree of haemodynamic significance on echocardiography.
†PDA (of any size) shunting right-left for >33% of cardiac cycle is suggestive of persistent pulmonary hypertension; therefore, will not be classified under any category above and will not be considered for the treatment.

Pharmacotherapy, when indicated (ie, for 'severe PDA' on echocardiography, irrespective of clinical symptoms, or a 'moderate PDA' on echocardiography with at least moderate clinical illness), is provided in the form of ibuprofen as a first-line agent at a standard dosing of 10 mg/kg followed by two doses of 5 mg/kg every 24 hours. The route of administration may be intravenous or enteral, as determined by the treating team. For treated infants, follow-up echocardiography is conducted at the end of the 3-day course, and a second course of treatment is initiated if they still fulfil study treatment criteria as mentioned above (table 2). If any treatment-eligible infant has a contraindication to ibuprofen as determined by the medical team, use of acetaminophen (15 mg/kg/dose every 6 hour for 3–7 days; intravenous or enteral) is permitted as an alternative agent.

Table 2 Approach to treatment in the intervention arm based on shunt volume and its clinical effects (SMART protocol)

Clinical	Echocardiography	Management plan
Mild	Mild	Observe
Mild	Moderate	Observe
Moderate	Mild	Observe
Severe	Mild	Observe
Moderate	Moderate	Treat
Any clinical stage	Severe	Treat

Control arm (early conservative management strategy)

Infants randomised to this arm do not undergo any further echocardiographic assessment or any pharmacological treatment of the PDA regardless of their clinical signs. If the infant gets an echocardiographic assessment for a reason different than study-related PDA assessment (such as hypotension or oxygenation failure or as a part of a separate clinical study) and a PDA is incidentally noted that fits the treatment matrix (table 2), the infant is not initiated on pharmacotherapy. After 7 days of age, decision on PDA assessment and treatment is at the discretion of the treating physician (figure 1).

Safety parameters for considering rescue management in the control arm

The presence of severe life-threatening clinical signs in infants in the control group that may prompt an echocardiography evaluation and PDA treatment are as follows: (a) pulmonary haemorrhage defined as blood-stained respiratory secretions with an acute significant increase in respiratory requirements (mean airway pressure >12 cm H_2O and/or fraction of inspired oxygen >60%);[24] (b) persistent systemic hypotension defined as mean blood pressure (in mm Hg) below the GA (in completed weeks) for >30 min.[24]

Study procedure

Consent and enrolment

Parents/guardians of eligible infants are approached for informed consent antenatally or within 72 hours of birth (sample consent form in online supplemental appendix C) (figure 1).

Randomisation

The unit of randomisation is the infant. Eligible preterm infants are randomised in a 1:1 ratio using computer-generated random numbers in randomly permuted blocks of 4 or 6. The study coordinator for each site randomises the infant using a secure RedCap-based application and notifies the neonatal intensive care unit (NICU) team caring for the infant.

Blinding

This is a pragmatic open-labelled trial aimed at assessing the feasibility of recruitment. Therefore, the care providers are not blinded to the allocation and are allowed to use other NICU interventions in both arms as per institutional protocol. These co-interventions are recorded for comparison. However, to protect from detection bias, the outcome assessors for the secondary clinical outcomes are blinded.

Outcome measures

Primary feasibility outcomes

(1) The proportion of eligible infants recruited during the study period, (2) the proportion of treatment outside of protocol-mandated therapy among randomised infants and (3) the proportion of infants in the control group meeting pre-defined safety criteria.

Secondary feasibility outcomes

(1) Reasons for non-recruitment for eligible infants and non-adherence to protocol, (2) completeness of data collection for clinical outcomes, (3) qualitative views of parents on recruitment and (4) inter-observer and inter-centre reliability of echocardiography measurements.

Secondary clinical outcomes

(1) Mortality during hospital stay, (2) procedural PDA closure, (3) proportion of infants receiving any PDA pharmacotherapy, (4) proportion of infants receiving open-label rescue medical treatment, (5) CLD (defined as the need for supplemental oxygen or respiratory support at 36 weeks of postmenstrual age),[25] (6) postnatal corticosteroid use for CLD, (7) pulmonary haemorrhage, (8) duration of invasive mechanical ventilation, (9) intraventricular haemorrhage (IVH; grades I to IV),[26] (10) severe IVH (grades III and IV),[26] (11) periventricular leukomalacia (any grade),[27] (12) NEC (stage 2 or greater),[28] (13) gastrointestinal bleeding within 7 days of the first dose of pharmacotherapy;, (14) spontaneous intestinal perforation, (15) severe retinopathy of prematurity (ROP) (stage 3 or greater),[29 30] (16) blood culture-confirmed sepsis, (17) oliguria (defined as <1 mL/kg/hour) and (18) duration of hospitalisation (days).

Health economic outcomes

(1a) Timeliness of access to costing data, (1b) similarity of costing methods across sites[2] and (2) evaluation of different cost-assessment approaches (ie, actual costs associated with care of infants in the trial, modelled costs based on historical data and resource use and modelled costs based on literature).

Sample size for pilot trial

Being a pilot study, the desired sample size was based on the sample required to reliably demonstrate feasibility. The criteria for success of the pilot study (feasibility measures) are defined in table 3.

Assuming a 70% recruitment of eligible infants and assuming a CI of 10% around this estimate to be acceptable,[31] the required sample size to demonstrate feasibility (ie, the lower bound of CI >60%) will be at least 100 infants. Similarly, assuming an 85% protocol adherence of randomised infants, to demonstrate protocol adherence feasibility (ie, the lower bound of CI >75%), a minimum of 77 infants will be required. Therefore, success of the feasibility study can be reliably demonstrated with a total sample size of 100 randomised infants.

Based on the consensus of the trial steering committee, the pilot RCT will be deemed 'definitely feasible' if we are able to recruit more than 60% of eligible infants during the study period and protocol adherence is demonstrated in more than 75% of randomised infants (table 3). The

Table 3 Criteria for considering feasibility

	Success criteria	
Primary feasibility outcomes	**Definitely feasible**	**May be feasibility**
Proportion of eligible infants enrolled for the study	>60%	40–60%
Proportion of randomised infants with no reported protocol deviations	>75%	65–75%

pilot RCT will be deemed 'may be feasible' if we are able to recruit 40–60% of eligible infants during the study period and protocol adherence is demonstrated in 65–75% of randomised infants. If the pilot RCT is deemed 'definitely feasible' or 'may be feasible' and no further protocol changes are mandated by the trial steering committee, all 100 participants may be rolled-over into the full-scale SMART-PDA trial. If a decision is made by the steering committee to modify the trial protocol in any form for the full-scale SMART-PDA trial, then data from the SMART-PDA pilot trial will be analysed as a separate standalone trial.

Data management

Data collection plan

All trial data are documented on a pre-specified case report form (CRF) and entered on a trial specific database through RedCap with participants identified only by their unique trial number. The database has been developed and maintained by RedCap and the SMART-PDA Research Team. Access to the database is restricted and secure. Any missing or ambiguous data are queried, ideally within 2 weeks of the query being raised. For infants with missing data (eg, if an infant has been transferred to another hospital and data have not been obtained from the continuing care site), data are obtained from the receiving hospital where possible. A secure link to an online questionnaire (RedCap) is sent to parents before discharge of the infant from the NICU. For parents who do not have internet access or prefer to complete a paper copy, a paper version is provided.

Source data management

In order to allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained. Source data are kept as part of the woman's and infant's medical notes generated and maintained at the site. Each site records the location of source data at their site using a source data location log. Data that are not routinely collected elsewhere are entered directly onto a paper CRF workbook or RedCap; in such instances, the CRF workbook or RedCap acts as source data, which is clearly defined in the source data location log. For this trial, source data refer to, though is not limited to, the woman's medical notes, infants' medical notes, women's and infants' local electronic case records, infant's echocardiography images and reports and parent questionnaires.

Data archiving

It is the responsibility of the principal investigator to ensure all essential trial documentation and source documents (eg, signed informed consent forms, investigator site files, participants' hospital notes, copies of CRFs etc) are securely retained for at least 25 years after the end of trial. No documents will be destroyed without prior approval from the trial steering committee.

Statistical analysis plan

Eligibility, recruitment and retention through the study will be presented in a CONSORT flow diagram.[17] The analysis will be by intention-to-treat with due emphasis on CI for between-arm comparisons. CIs will be interpreted within a descriptive compatibility framework and will not be used for inference or incorporated in a formal stopping rule. Descriptive statistics of demographic and clinical measures will be used to assess balance between the randomised arms at baseline, but no formal statistical comparisons will be made.

The primary feasibility outcomes will be expressed as proportions. For secondary clinical outcomes, a Bayesian analysis will be conducted to explore the posterior probability of benefit or harm, along with the corresponding 95% credible intervals (CrIs). Prior probabilities obtained from the most recent Cochrane review of early treatment versus expectant management of the PDA in preterm infants will be used for the Bayesian analysis.[32] Our previous work demonstrated that parents view death, severe IVH, NEC and CLD as critical for their child's well-being.[33] Hence, we plan to develop a series of binomial models for each of these outcomes and then conduct a stochastic multicriteria acceptability analysis incorporating partial utilities estimated by swing weights for the said outcomes based on our previous work to determine the probability of net positive benefit with the SMART approach.[34] The rationale for conducting the Bayesian analysis is to aid stakeholders including clinicians and parent partners decide on appropriateness of enrolling this vulnerable population in a larger trial with similar methodology if the feasibility of recruitment in the pilot trial is established. The posterior probabilities obtained from the Bayesian analysis is not intended to be used for clinical decision-making. A thematic analysis approach will be used to qualitatively analyse the views of parents on enrollment of their infants born at <26 weeks of GA in this trial.[35]

Given that estimation of effectiveness of the SMART protocol is not the primary objective of this trial, we do not plan to conduct any interim analysis or set any 'statistical stopping rules'. Therefore, all analyses will be done at the end of the recruitment period. All secondary outcomes, in addition to the feasibility outcomes, will be reported for inclusion in meta-analyses updates. Table 4 summarises the analysis plan for all stated primary and secondary objectives.

For the larger definitive trial, which will be informed by this pilot trial, assuming a baseline risk of 80% for death/CLD (2019 CNN data),[25] to demonstrate superiority of the SMART approach over conservative management (10% absolute risk reduction of death/CLD), we will require a minimum of 588 infants (with a two-sided α of 0.05 and power of 80%).

Safety considerations

Data safety monitoring board (DSMB)

A DSMB has been set up comprising of two neonatologists and a biostatistician who are not study investigators

Table 4 Summary of the study objectives, outcomes and analysis plans

Objectives	Outcomes	Analysis plan
Assess the feasibility of recruitment, protocol adherence, diagnostic accuracy and data completion	Rate of recruitment of eligible infants, proportion of randomised infants with no protocol violation and proportion of infants with missing clinical outcome data	Descriptive statistics: mean (SD) or median (IQR) for continuous variables and proportions for dichotomous variables
Reasons for non-recruitment and non-adherence to protocol; **views of parents** on recruitment	Qualitative study feedback	Qualitative results based on thematic analysis (using Braun and Clarke's approach)
Assess clinical outcomes that will form primary and secondary outcomes for the larger RCT	Mortality and major morbidities as outlined in the 'outcome measures' section	Bayesian analysis with prior probabilities obtained from the most recent Cochrane review of early treatment versus expectant management of the PDA (along with the corresponding 95% credible intervals)
Feasibility of cost-effectiveness 1. Quality of routinely captured costing data 2. Need for and feasibility of micro-costing poorly captured components of existing costing data	1. (a) Timeliness of access to costing data and (b) similarity of costing methods across sites 2. Evaluation of different cost-assessment approaches (ie, actual costs associated with care of infants in the trial; modelled costs based on historical data and resource use; modelled costs based on literature)	1. Descriptive summary of costing methods and availability at participating sites 2. Qualitative consensus on best approach for cost-effectiveness analysis among trial steering committee members using the Delphi process

and are free of any financial or intellectual conflicts of interest. The DSMB meets every 6 months (or earlier if deemed necessary) to ensure the overall safety of patients in the SMART-PDA pilot trial based on a review of the totality of evidence and the principle of the emergence of proof beyond a reasonable doubt that is likely to influence clinical practice, thereby minimising avoidable harm and maximising benefit.

Reporting of serious adverse events (SAEs)

For this study, an SAE is defined as one that results in death, is life-threatening or results in persistent or significant disability or incapacity. Potential SAEs include death, NEC (stage 2 or 3), gastrointestinal perforation and severe IVH (grades 3 and 4). Specific SAEs are recorded and reported to the institutional research ethics committee as soon as it occurs expeditiously, according to institutional regulatory reporting requirements for the duration of the study (36 weeks of corrected GA or discharge from the study site NICU, whichever is later). Reports on SAEs are also sent to the DSMB within 72 hours of diagnosis. In addition, all serious unexpected adverse drug reactions with respect to the use of ibuprofen or acetaminophen that has occurred inside or outside Canada are reported to Health Canada as follows:

a. If it is neither fatal nor life threatening, within 15 days after becoming aware of the information.
b. If it is fatal or life threatening, within 7 days after becoming aware of the information.

Trial management

Trial oversight is conducted by the Trial Steering Committee that is comprised of a team of experienced neonatal clinical trialists, early career investigators in neonatology, biostatisticians, a paediatric cardiologist and a parent partner representative. The members of the trial steering committee are listed in online supplemental appendix D. Safety of trial participants is monitored by an independent Data Safety Monitoring Board as mentioned above.

Trial monitoring

The trial is being carried out in accordance with the Declaration of Helsinki in its latest form and the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. The site investigator consents to data evaluation being performed by the monitoring team (comprising the PI and his delegates) to ensure satisfactory data collection and adherence to the study protocol. A summary of the protocol amendments to date and the corresponding explanations are outlined in online supplemental appendix E. The tasks of the site investigator include maintenance of the source data as comprehensively as possible; this includes information concerning medical history, accompanying diseases, inclusion in the trial, data about visits, results of imaging and investigations, dispensing of medication and adverse events. The monitoring team is also permitted to perform data evaluation and draw comparisons with the relevant medical files in accordance with the standard operating procedures and ICH-GCP guidelines at predetermined intervals to ensure adherence to the study protocol and continuous registration of data. All original medical reports required as sources for the information given in the CRF may be inspected. The substitute decision makers of the study participants will have given their consent to such inspection by signing the consent form.

The monitoring team members are obliged to treat all information as confidential and to preserve the basic claims of the study participants in respect of integrity and protection of their privacy.

Anticipated challenges and solutions

We have thought of and planned for challenges likely to be faced in our study design and execution: *(1) Risk of performance bias due to lack of blinding:* we acknowledge that co-interventions may be different in the two groups due to lack of blinding of NICU staff. However, the objective of the main trial is not to test the efficacy of ibuprofen for PDA closure (which has already been proven in previous placebo-controlled RCTs).[8] Rather we intend to pragmatically test the effectiveness of an early selective treatment approach in improving clinical outcomes while allowing usual NICU care. If the larger RCT shows that similar patient-important clinical outcomes can be achieved with usual supportive NICU care without ibuprofen exposure even in extremely preterm infants with a symptomatic PDA, this will help to minimise early exposure of infants to these harmful medications; *(2) Variation in echo diagnosis:* Standardised echo assessments (online supplemental appendix B) are used across participating centres to minimise diagnostic variation.

ETHICS AND DISSEMINATION

The study has been approved by the IWK Research Ethics Board (#1027298) and six additional participating sites at the time of publication of this protocol.

Our integrated knowledge translation (KT) and end-of-study KT objectives and strategies are outlined as follows:

Integrated KT: (a) *involvement of stakeholders in protocol development* by organising regular virtual meetings before proposal submission for grant and ethics applications and (b) *engagement of local site investigators for protocol adherence* by organising quarterly virtual meetings and by development and dissemination of infographics of the study protocol to all participating sites.

End of study KT: (a) *dissemination of results* to wider Canadian and international neonatal community by presenting results at the Canadian Paediatric Society and Paediatric Academic Society's Annual Meeting. The primary objective of end-of-grant KT will be to seek interest in the larger definitive trial from all stakeholders including clinicians and parent groups; (b) publication of results in peer-reviewed journals; (c) *updating existing Cochrane review* with trial results; (d) *develop steering committee* for the larger trial and involve parent representatives for outcome prioritisation; and (e) seek funding opportunities for the main RCT.

DISCUSSION

PDA management remains one of the most controversial topics in neonatal intensive care with polarised opinions regarding treatment despite over 80 RCTs on this topic. This is likely attributable to two major limitations of existing RCTs: (a) lack of representation of the most vulnerable preterm infants at the highest risk of PDA attributable morbidity and (b) limitations in current definitions of haemodynamically significant PDA.

Most previous trials have included mature infants, with a mean GA of>26 weeks in 97% trials. Interestingly, a follow-up analysis of eligible infants who were not enrolled in the recently published PDA-TOLERATE trial due to the lack of physician equipoise showed that the group treated before 6 days postnatal age had a significantly lower incidence of CLD and CLD/death despite having lower GA, less receipt of antenatal steroids and substantially higher respiratory morbidity.[36] These findings suggest that exposure to a moderate-large PDA shunt for ≥1 week in an extremely preterm infant could lead to adverse clinical outcomes such as CLD or death, irrespective of later PDA treatment. Further, the eligibility criteria with respect to hs-PDA definition have been wide, thus creating substantial heterogeneity in existing RCTs. A PDA size of >1.5 mm and the left atrium to the aortic root (LA:Ao) ratio of >1.4 have been the two most commonly used measures to define haemodynamic significance in RCTs.[7 37] The major problem with this approach is that it does not differentiate between a moderate and a severe PDA shunt and completely ignores the clinical effects of the shunt volume. Martins *et al* demonstrated that the PDA size itself is weakly correlated to shunt volume.[20] Furthermore, a PDA of a particular size may have a variable haemodynamic effect based on the infant's pulmonary mechanics. This could possibly explain why the Beneductus trial, which enrolled preterm infants born at <28 weeks of GA with a left-to-right shunting PDA of any size of >1.5 mm, failed to demonstrate the benefits of early pharmacotherapy despite enrolling the smallest and sickest patients.[13] Clyman *et al*, in a secondary analysis of their PDA-TOLERATE trial, demonstrated that prolonged exposure to a moderate-large PDA shunt (≥ 11 days) was associated with an increased risk of CLD, only in infants who received prolonged mechanical ventilation (≥10 days).[38] Similarly, a secondary analysis of the TRIO-CAPI trial also showed that moderate-large PDAs were associated with an increased risk of death or CLD only when infants required intubation for more than 10 days.[39] Therefore, it is important to consider the clinical effects of PDA shunt in addition to echocardiography-confirmed markers of a large shunt volume on the preterm infant to identify PDA shunts that might benefit from closure.

The SMART-PDA trial attempts to address both the above-mentioned gaps in knowledge by exclusively enrolling the smallest preterm infants born at <26 weeks of GA and incorporating both clinical and echocardiographic criteria in its early treatment strategy. The proposed pilot trial will provide us with a valuable opportunity to explore the feasibility of conducting such a trial on a larger scale. The data generated from this pilot trial may further help us refine the highest risk population and, if required, incorporate prognostic or predictive

enrichment strategies in the design of the definitive trial to decrease heterogeneity and improve the statistical power to detect a clinical meaningful effect within a reasonable timeframe.

CONCLUSION

There is limited evidence on whether, in the extremely preterm infants with a PDA, a selective early treatment strategy based on clinical and echocardiographic markers of moderate/severe shunt volume versus no treatment in the first postnatal week improves clinical outcomes. The SMART-PDA pilot trial will provide an opportunity to explore if such a trial is feasible in extremely preterm infants born at <26 weeks of GA who remain at high risk of adverse clinical outcomes despite recent advances in neonatal intensive care.

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Contributors SM conceived the project, is the Principal Applicant on all related research grants, drafted the manuscript and is responsible for the overall content as guarantor. AHé provided expert input in the development of the project and reviewed the manuscript draft. MC provided expert input in the development of the project and reviewed the manuscript draft. TD drafted the statistical analysis section of the manuscript. WE-N provided expert input in the development of the project and reviewed the manuscript draft. SD provided expert input in the development of the echocardiography protocol and reviewed the manuscript draft. ZA provided expert input in the development of the project and reviewed the manuscript draft. JK provided expert input in the development of the project and reviewed the manuscript draft. ACK provided expert input in the development of the project and reviewed the manuscript draft. AHy provided expert input in the development of the project and reviewed the manuscript draft. KK provided expert input in the development of the project and reviewed the manuscript draft. MM provided expert input in the development of the project and reviewed the manuscript draft. DEW provided expert input in the development of the project, reviewed the manuscript draft. AJ provided expert input in the development of the project and reviewed the manuscript draft. FB is a patient partner who provided input on outcome prioritisation for the trial and reviewed the manuscript draft. AC was the primary research coordinator involved in trial oversight and day-to-day trial operations until July 2023 and reviewed the manuscript draft. TH is currently the primary research coordinator involved in trial oversight and day-to-day trial operations and reviewed the manuscript draft. JD provided expert input in the development of the project and reviewed the manuscript draft. PJM provided expert input in the development of the project and reviewed the manuscript draft. LT provided expert input on the statistical analysis section of the manuscript and reviewed the manuscript draft.

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Appendices

Table of Contents

Appendix A. WHO Trial Registration Data Set

Primary Registry and Trial Identifying Number	ClinicalTrials.gov ID NCT05011149
Date of registration	August 18th, 2021
Secondary Identifying Numbers	459750
Source(s) of Monetary or Material Support	This work was supported by the Canadian Institutes of Health Research (CIHR) Early Career Investigators in Maternal, Reproductive, Child and Youth Health Grant 2020 with 1:1 matching fund support from the Dalhousie Medical Research Foundation; IWK Health Research; Department of Pediatrics, Dalhousie University.
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Public Title	Selective Early Medical Treatment of the Patent Ductus Arteriosus in Extremely Low Gestational Age Infants: A Pilot Randomized Controlled Trial
Scientific Title	Selective Early Medical Treatment of the Patent Ductus Arteriosus in Extremely Low Gestational Age Infants: A Pilot Randomized Controlled Trial (SMART-PDA)
Countries of Recruitment	Canada and the United States of America
Study objectives	The overall purpose of this pilot study is to assess the feasibility of conducting a large study to explore the following research question: "In preterm infants born <26 weeks' gestational age, does a strategy of selective early treatment of a moderate-severe patent ductus arteriosus (PDA) shunt in the first week of life lead to reduction in the composite outcome of death or severe chronic lung disease (CLD) when compared to an early conservative management strategy?" The ***specific primary (feasibility) objectives*** of this pilot study are to assess: (a)

	The proportion of eligible infants enrolled in the trial (b) The proportion of treatment outside of protocol-mandated therapy among enrolled infants. The ***secondary objectives*** are to (a) assess the nature of treatment outside of protocol-mandated therapy; (b) views of parents/guardians on enrollment in this RCT; (c) compare clinical outcomes between the planned comparison groups; (d) assess the feasibility of conducting a cost-effectiveness analysis for the main trial
Planned Trial Interventions	**Experimental group [Selective early medical treatment (SMART) strategy]:** Selective early pharmacological treatment of a moderate-severe PDA shunt (identified based on pre-defined clinical signs & routine screening echocardiography) within the first 72h of life with provision for repeat treatment if moderate-severe shunt persists **Control group [Early conservative management strategy]:** No treatment of PDA in the first one week after birth
Inclusion criteria	Preterm infants born less than 26 completed weeks (i.e., up to and including 25 weeks and 6 days) of gestation with a PDA diagnosed on screening echocardiography performed within 72h of birth. Infants receiving prophylactic cyclo-oxygenase inhibitor therapy (indomethacin, ibuprofen or acetaminophen) will be eligible for inclusion if the screening echocardiography is performed after completion of the course of prophylactic cyclo-oxygenase inhibitor drug but before 72h of age.
Exclusion criteria	No PDA diagnosed on initial screening echocardiography; congenital heart disease (excluding patent foramen ovale, atrial septal defect or ventricular septal defect with a defect size less than 2mm); other major congenital anomaly; decision to withhold/withdraw care
Study Type	Multi-center, open-label, pragmatic, parallel-design pilot randomized controlled trial
Date of First Enrollment	January 10th, 2022
Sample size	Anticipated: 100 randomized infants Enrolled (as of April 24th, 2024): 87 infants randomized
Recruitment Status	Recruiting
Outcomes	***Primary feasibility outcomes:*** (1) Proportion of eligible infants recruited during the study period; (2) Proportion of randomized infants with no reported treatment outside of protocol-mandated therapy; (3) Proportion of infants in control group meeting pre-defined safety criteria ***Secondary feasibility outcomes:*** (1) reasons for non-recruitment and non-adherence to protocol; (2) completeness of data collection for clinical outcomes; (3) qualitative views of parents/guardians on recruitment; (4) inter-observer and inter-center reliability of echocardiographic measurements

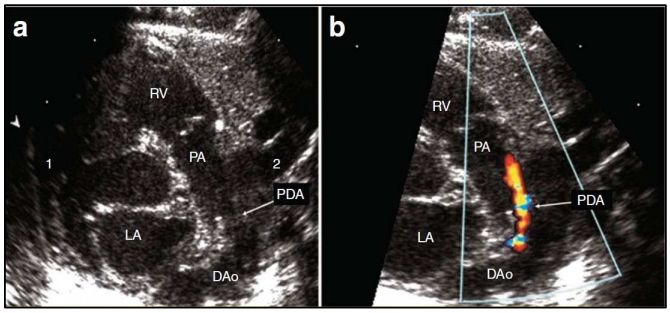
	Secondary clinical outcomes: (1) Mortality during hospital stay; (2) procedural PDA closure; (3) proportion of infants receiving any PDA pharmacotherapy; (4) proportion of infants receiving open-label rescue medical treatment; (5) CLD (defined as need for supplemental oxygen or respiratory support at 36 weeks' postmenstrual age); (6) postnatal corticosteroid use for CLD; (7) pulmonary hemorrhage; (8) duration of invasive mechanical ventilation; (9) Intraventricular hemorrhage (IVH) (grades I to IV); (10) Severe IVH (grades III and IV); (11) Periventricular leukomalacia (any grade); (12) Necrotizing enterocolitis (NEC; stage 2 or greater); (13) Gastrointestinal bleeding within seven days of the first dose of pharmacotherapy; (14) Spontaneous intestinal perforation; (15) Severe retinopathy of prematurity (ROP) (stage 3 or greater); (16) Blood culture confirmed sepsis; (17) Oliguria (defined as < 1 mL/kg/hour); (18) Duration of hospitalization (days) ***Center-level health economic outcomes:*** (1) Qualitative assessment of routinely captured NICU costing data in each participating center
Ethics Review	• IWK REB # 1027298 (approved October 13, 2021) • Comité d'éthique de la recherche (CER) du CHU de Québec-Université Laval: Projet# 2022-6116 (approved February 16, 2022) • UBC C&W Research Ethics Board: #H22-00010 (approved July 12, 2022) • Sharp Institution Review Board: #2111901 (approved June 10, 2022) • The Children's Hospital of Orange County In-House (CHOC IH) IRB: #220461 (approved November 15, 2022) • University of Oklahoma Health Sciences Center's Institutional Review Board (IRB): # 16663 (approved February 3rd, 2024) • The University of Alberta Health Research Ethics Board (HREB): #Pro00116512 approved August 9, 2023
Anticipated completion date	August 31st, 2024
IPD sharing statement	Plan to share IPD: Yes Plan description: Technical appendix, statistical code, and dataset available will be published in an online repository and will be available upon reasonable request.

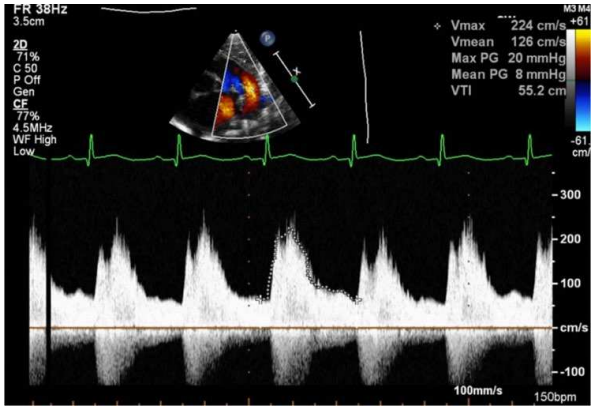
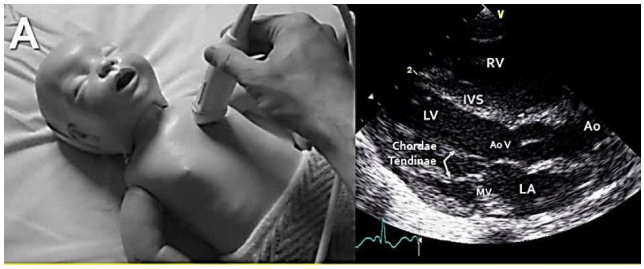
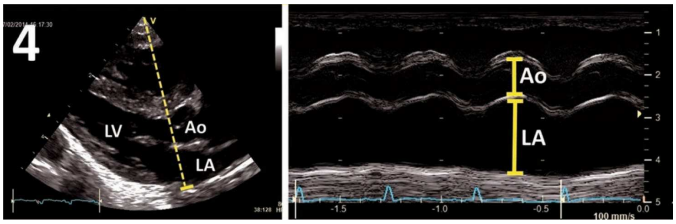
Appendix B. Standardized echocardiographic assessment of the patent ductus arteriosus (PDA)

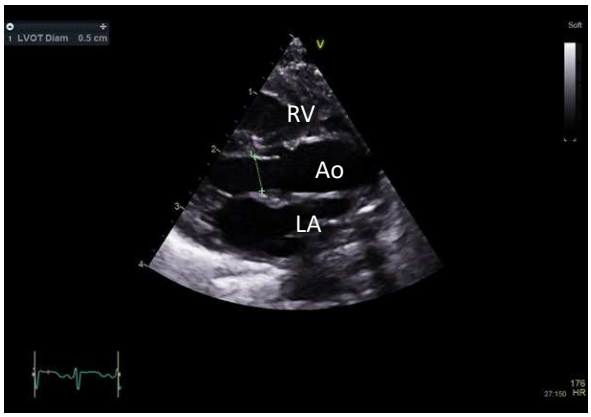
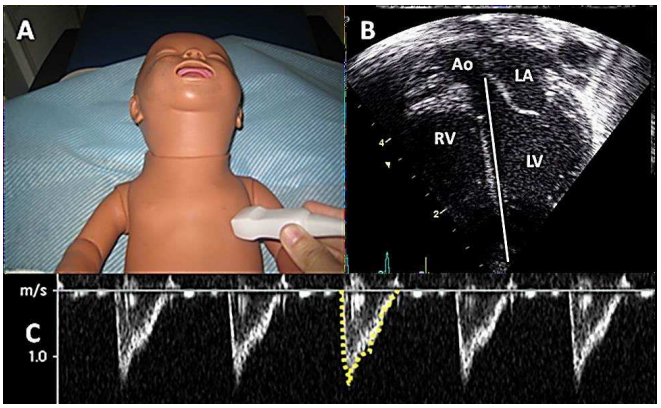
All participating centers are a part of the Neonatal Hemodynamics Research Centre (https://www.neonatalhemodynamics.com/index.html). All participating centers follow standardized protocols for echocardiographic image acquisition and measurements. These protocols have been devised following the guidelines and training recommendations outlined by the American Society of Echocardiography (ASE) in collaboration with the European Association of Echocardiography (EAE), the Association for European Pediatric Cardiologists (AEPC) and the European Special Interest Group 'Neonatologist Performed Echocardiography' (NPE).

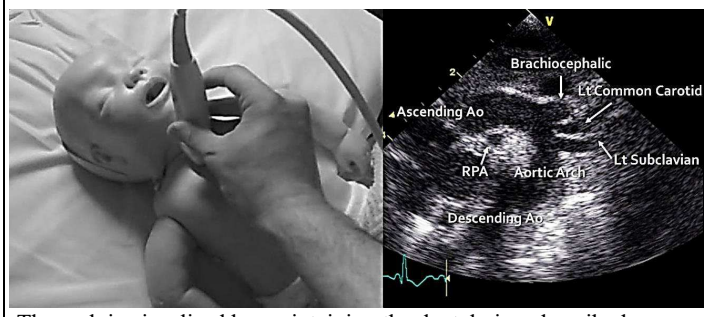
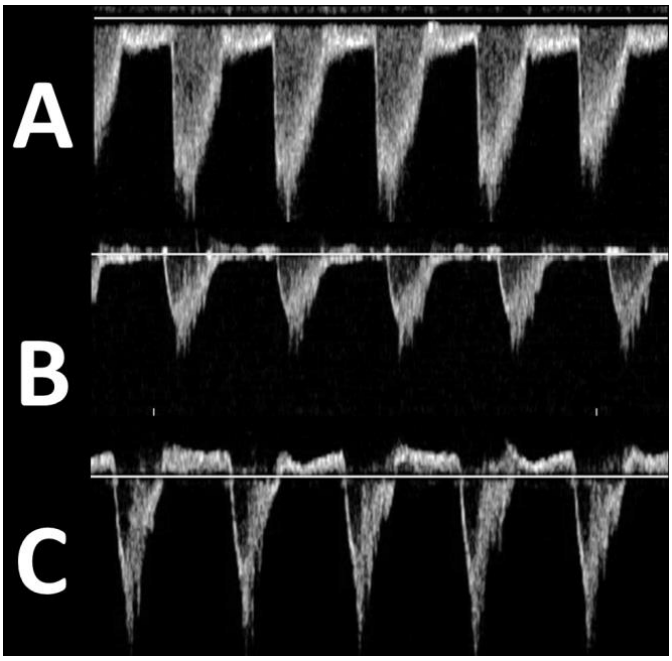
The image acquisition techniques and measurement guidelines specific to PDA assessment in this RCT are outlined as follows:

Echo parameter	Image Acquisition	Key points for image acquisition & measurement	Visual guide for image acquisition & measurement*

PDA diameter	***Window:*** High 'left sided' parasternal (ductal view)
	
	Axis/plane: Short axis
	
	Focus: PDA sweep
		• B-Mode and color doppler **must be done simultaneously** for the PDA sweep
		  ○ Sweep: Start at the aortic arch and go towards PA
		  ○ Color scale ~60 cm/s
		• If PDA Doppler does not have a straight angle, it is possible to angle posterior from branch PA view to obtain good images of the PDA => ***Alternate DA view***
		• Measurement of the PDA **must be done with B-Mode images**
		• ***PDA Size:***
			
			The picture demonstrates probe position, and the echo image shows the corresponding view. The PDA is seen to connect the descending aorta (DAo) to the pulmonary artery (PA).
			 
			PDA diameter (a: 2D; b: color doppler)

		narrowest point along the ductal length, when the shunt is at its peak during cardiac cycle	
PDA direction of flow and peak systolic velocity	***Window:*** High 'left sided' parasternal (ductal view) ***Axis/plane:*** Short axis ***Focus:*** PDA sweep	• Pulsed wave/ Continuous wave doppler at narrowest point to be able to measure the peak systolic velocity and to evaluate the direction of flow ○ Mean of 3 measures **must be taken** for the peak systolic velocity assessment	
Left atrium to aortic root (LA:Ao) ratio	***Window:*** parasternal ***Axis/plane:*** long axis ***Focus:*** M-mode through aortic valve leaflets with line of interrogation perpendicular to aorta	M-Mode: • Line of interrogation should be perpendicular to aorta and LA • Aortic valve must be visible	 The probe is placed perpendicular to the chest, left of the lower third of the sternum, with the probe marker pointing towards the right shoulder (A). The corresponding image of the heart illustrates the left heart structures  The image demonstrates the line of interrogation perpendicular to aorta and LA and the corresponding M-mode image

Left ventricular output	***Aortic valve (AV) annulus*** ***Window:*** parasternal ***Axis/plane:*** long axis ***Focus:*** Aortic valve annulus ***Aortic velocity-time integral (VTI)*** ***Window:*** Apical ***Axis/plane:*** 5 chamber view ***Focus:*** LV outflow	***Aortic valve annulus*** •B-Mode with narrow window on aortic valve and LA •Measure the AV annulus from hinge point to hinge point at end-systole (just before valve closure) ***Aortic VTI*** •Narrow image to LVOT •Open LVOT with some anterior angulation (+/- clockwise rotation) •Aorta must be well opened •Color scale 70-80 cm/s •For VTI measurement: i) Pulsed wave doppler with B-Mode ii) Sample volume at the level of the aortic valve iii) Keep angle of isonation to a minimum for accurate aortic VTI. iv) May need to use TILT button to improve the angle of isonation *Calculation of LV output* LVO (ml/kg/min) = $(\boldsymbol{AoCSA}^{**} \times \boldsymbol{VTI} \times \boldsymbol{Heart\ Rate}) / \boldsymbol{Weight}$ **AoCSA (aortic valve annulus cross-sectional area) = 3.14 x (Aortic valve annulus diameter)^2/4	**Aortic valve annulus (parasternal long axis view)**  **Measurement: Aortic VTI (5 Chamber View)**  Probe position (A) and 5 chamber (apical long axis) view of the heart (B). A pulsed wave Doppler measures blood flow across the aortic valve (white lines). The area under the curve is then traced to obtain the VTI (C) (yellow line).

Diastolic flow pattern in descending aorta	***Window:*** Suprasternal ***Axis/plane:*** Short axis ***Focus:*** Descending aorta	Colour Doppler should be used to demonstrate arch flow. **The pulsed wave Doppler should be placed 1 cm below the opening of the PDA if present**	 The arch is visualised by maintaining the ductal view described previously, moving the probe slightly to the right of the sternum, and rotating the probe in slight clockwise fashion  Panel (A) demonstrates forward flow in diastole. Panel (B) demonstrates the presence of absent diastolic flow. Panel (C) shows reversed diastolic flow

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2. van Laere D, van Overmeire B, Gupta S, El-Khuffash A, Savoia M, McNamara PJ, Schwarz CE, de Boode WP; European Special Interest Group 'Neonatologist Performed Echocardiography' (NPE). Application of NPE in the assessment of a patent ductus arteriosus. Pediatr Res. 2018 Jul;84(Suppl 1):46-56. doi: 10.1038/s41390-018-0077-x. PMID: 30072803; PMCID: PMC6257219.

*__Images obtained__ from the "Neonatologist Performed Echocardiography Teaching Manual", 2019 Edition. Edited by Afif El-Khuffash, Neonatologist, The Rotunda Hospital, Dublin, Ireland, Clinical Professor of Paediatrics, Royal College of Surgeons in Ireland [https://www.neonatalhemodynamics.com/PDF/NPE_Teaching_Manual_El-Khuffash_%202019.pdf]

Appendix C. Informed Consent Form

Informed Consent Form

Research Study Participation

Study Title: Selective Early Medical Treatment of the Patent Ductus Arteriosus in Extremely Low Gestational Age Infants: A Pilot Randomized Controlled Trial

Short Title: The SMART PDA Pilot Trial

Principal Investigator: Dr. Souvik Mitra
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Funding: Canadian Institutes of Health Research (CIHR), Dalhousie University Faculty of Medicine, Dalhousie Medical Research Foundation (DMRF), Department of Pediatrics Dalhousie University, IWK Research

INTRODUCTION

You are being invited to take part in the research study named above on behalf of your infant(s). This form provides information about the study. Before you decide if you want your baby to take part, it is important that you understand the purpose of the study, the risks and benefits, and what you will be asked to do. Taking part is entirely voluntary (your choice). Informed consent starts with the initial contact about the study and continues until the end of the study. A member of the research team will be available to answer any questions you have. You may decide not to have your baby take part, or you may withdraw your baby from the study at any time. This will not affect the care you or your family members receive at IWK Health in any way.

WHY ARE THE RESEARCHERS DOING THE STUDY?

The purpose of this study is to compare two commonly used treatment approaches for Patent Ductus Arteriosus (PDA). PDA is the most common heart problem in extremely preterm babies (those born less than 26 weeks of gestational age). PDA occurs when the ductus arteriosus (a blood vessel that

connects two major arteries coming out of the heart) does not close after birth. In full-term babies, the ductus arteriosus typically closes 24-72 hours after birth. In preterm babies, this closure may not occur as quickly, or at all, leading to PDA. Eventually most PDAs in preterm babies close on their own. But in babies born extremely preterm, this closure may take a very long time. If an extremely preterm baby remains exposed to a PDA for a long time, it may affect the health of the baby. The PDA, if untreated, may increase the risk of lung damage (also known as chronic lung disease), damage to the gut (known as necrotizing enterocolitis, which in some cases may require surgery), and even death.

Due to these risks, doctors use different strategies to close a PDA, that include treating with a medication or closing the PDA using surgery or catheter if medical treatment fails or cannot be done. The medication that is most commonly used to treat a PDA is ibuprofen, the same medication that adults often take for pain control. But there are risks to giving this medication to an extremely preterm baby. These risks include risk of damage to the kidneys and gut. Therefore, some doctors prefer to do an echocardiogram (a type of ultrasound that looks at the heart) early within the first 2-3 days after birth. The use of echocardiograms has been shown to be safe for extremely preterm babies. The purpose would be to treat only those babies with a large PDA that is less likely to close on its own. This early approach helps to selectively treat only those who need treatment with ibuprofen.

Some doctors choose to wait and watch for a few days and use ibuprofen only when there are signs that the PDA is still open and is causing breathing or feeding problems. The benefit of this approach is that fewer preterm babies are exposed to the side effects of ibuprofen. However, the downside is that this 'wait and watch' approach may be too late for those who need medication. Waiting and watching even for a few days might be harmful for the extremely preterm babies as the PDA may cause permanent damage even in the first week after birth.

While the approach of 'waiting and watching' has not yet been directly linked to poor outcomes, no research has ever been done to compare these two approaches (selective early treatment versus wait-and-watch approach) in babies born extremely preterm to find out which one is safer and better. Since both approaches are commonly practiced in the NICU based on the preference of the care team, and babies born less than 26 weeks of gestational age are at a high risk of lung problems, gut problems. kidney issues, and death, we feel doing this research to compare these two treatment strategies can significantly improve the outcomes of these extremely preterm babies.

HOW WILL THE RESEARCHERS DO THE STUDY?

This is a multi-site study taking place at 6 Neonatal Intensive Care Units (NICUs) across Canada and in the Unites States. This study will be carried out as a randomized controlled study, which is a clinical study where participants are randomly put into one of two treatment groups. This study will be carried out as a pilot randomized study where we are estimating that 100 premature babies (born less than 26 weeks of gestational age) will take part. If we find that it is feasible to enroll 100 babies and properly conduct this study across these 6 centers within a reasonable time frame, we will go on to conduct a larger study with approximately 600 extremely preterm babies across several NICUs in Canada and the United States.

If you decide to have your baby take part in this study, they will receive an echocardiogram to determine if they have PDA. If echocardiogram shows a PDA, your baby will be randomized into 1 of 2 care approaches (SMART PDA approach or Conservative management approach)

1) SMART PDA: The SMART PDA approach is a set of treatment guidelines that consider both echocardiogram results and clinical signs (physical symptoms your baby shows, such as needing oxygen) to decide the PDA treatment plan for the first week of life. These guidelines allow the care team to identify whether the clinical and echocardiogram features are Mild, Moderate or Severe. Based on these ratings a PDA treatment plan is chosen.

   If your baby meets the criteria for treatment they will receive medication to treat the PDA (typically ibuprofen). After 3 days of treatment they will receive another echocardiogram to reassess their PDA. If necessary, a second round of treatment will take place. After the first week, your baby will no longer be a part of the study and your baby's care team will continue to treat the PDA at their discretion. Table 1 provides you with the SMART PDA treatment plan.

Table 1:

Clinical Symptoms	Echocardiogram Results	Treatment Plan
Mild	Mild	Observe
Mild	Moderate	Observe
Moderate	Mild	Observe
Severe	Mild	Observe
Moderate	Moderate	Treat
Any clinical stage	Severe	Treat

2) Conservative management: If your baby is randomized to this group, they will not receive any further study related echocardiograms in the first week after birth. They may receive echocardiograms for other reasons unrelated to the study. Your baby will not receive any medications or surgery to treat the PDA for the first week of life. After this week your baby will no longer be a part of the study and PDA treatment will be based on your care teams' approach.

To ensure safety of every baby participating in the study, in the event that your baby shows severe symptoms that might be related to a PDA, your care team may choose to get an echocardiogram for your baby and may move ahead with PDA treatment, regardless of your study involvement.

Both the babies in the SMART PDA group as well as the conservative management group will have health information collected during their hospital stay. This information will be entered into a secure database and the baby will only be identified using their study number. Additionally, we are asking families to complete a short questionnaire about their participation in this study when the baby reaches 36 weeks corrected age or before their discharge/transfer (whichever comes first).

WHAT ARE THE BURDENS, HARMS AND POTENTIAL HARMS?

At the IWK NICU, the treatment approaches outlined in both study groups are currently used for treatment of the PDA. As a part of usual clinical care at the IWK NICU, some doctors choose to get an echocardiogram of the heart early within the first 1-3 days and treat the PDA early if they feel treatment is necessary. Other doctors choose to wait and watch a bit longer and treat the PDA only when your baby shows definite signs of breathing or feeding problems, or heart or kidney issues related to the PDA. Regardless of when the doctors decide to treat the PDA, ibuprofen is used as the standard first choice treatment at the IWK NICU. Many babies require multiple courses of ibuprofen

treatment to close the PDA. Follow-up echocardiograms are done following a course of treatment when the baby still shows signs that the PDA is open and large.

Therefore, regardless of your participation in this study, your baby will likely receive one of these two treatment approaches, based on the preference of your care team. If your baby is in the SMART-PDA arm, your baby will get at least two more echocardiograms during the course of the first week to look for a large PDA so that it can be treated early. The use of echocardiograms has been shown to be safe for extremely preterm babies. Therefore, we do not think taking part in this study puts your baby at any additional risk of harm from being part of a research study. It is important that we acknowledge the possibility of unforeseen risk. In the event that your baby shows severe, life threatening symptoms that may or may not be related to the PDA, the care team will initiate necessary treatment regardless of the study group.

WHAT ARE THE POSSIBLE BENEFITS?

At this point we do not know which treatment approach is better than the other, if at all, in extremely preterm babies. If one approach is truly better than the other, then your baby will have a 50% chance of being in the better treatment group, which will benefit your baby directly. We also hope the information learned from this study will help other preterm babies in the future.

WHAT ALTERNATIVES TO PARTICIPATION DO I HAVE?

You do not have to allow your baby to participate in this study. Choosing not to participate will in no way affect your, or your baby's, care at IWK Health or any other hospital. If you choose not to participate your baby will still receive similar PDA treatment practices because both treatment approaches are standard care across NICUs.

CAN I WITHDRAW FROM THE STUDY?

You can choose to withdraw your baby from the study at any time without providing a reason. If you choose to withdraw from the study, you are encouraged to contact the study doctor or study staff listed on the first page of this document.

Information that was recorded before you withdrew will be used by the researchers for the purposes of the study, but no information will be collected after you withdraw your permission.

WILL THE STUDY COST ME ANYTHING AND, IF SO, HOW WILL I BE REIMBURSED?

Taking part in this study will not cost you, or your family, anything.

ARE THERE ANY CONFLICTS OF INTEREST?

There are no conflicts of interest.

WHAT ABOUT POSSIBLE PROFIT FROM COMMERCIALIZATION OF THE STUDY RESULTS?

No profit will be made from commercialization of the study results.

HOW WILL MY PRIVACY BE PROTECTED?

If you decide to let your baby take part in this study, the study doctors and study staff will only collect the information they need for this study. Records identifying you and your baby will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Your baby's information will be kept strictly confidential. Your baby will be given a study ID number which will be used on all other study documents except for this consent form. Your baby's name, address or other information that may directly identify you or your baby will not be used. A copy of this signed consent form will be included in your baby's health record/hospital chart. All study documentation will be securely stored and password protected.

If the results of this study are published, your identity, and your baby's, will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published and/or presented to the scientific community at meetings and in journals.

Data from the study will be securely stored for 10 years past the age of child's maturity, as per IWK Health guidelines.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated.

WHAT IF I HAVE STUDY QUESTIONS OR PROBLEMS?

Your baby's care team is available to answer any questions regarding the care your baby is receiving. If you have questions or concerns regarding this study and your involvement, or if you suffer a research-related injury, you can talk to the doctor who is in charge of the study at this institution – Dr. Souvik Mitra (902-470-7426)

The Research Ethics Board at IWK Health has reviewed this study. If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call Joanne Street, IWK Health Research Ethics Board (902-470-7879).

WHAT ARE MY RESEARCH RIGHTS?

If you choose to allow your baby to take part in this research study in no way does this waive your legal rights nor release the investigator(s), sponsors, or involved institution(s) from their legal and professional responsibilities. If you or your baby becomes ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. You are free to withdraw from the study at any time without jeopardizing the health care you and your baby are entitled to receive. If you have any questions at any time, during or after the study, about research in general you may contact the Research Office of IWK Health at (902) 470-7879, Monday to Friday between 8:00 am. and 4:00 pm.

HOW WILL I BE INFORMED OF STUDY RESULTS?

A summary of the study results can be sent to you once the study is complete and the data has been analyzed.

I would like to receive a copy of the study results. ☐ Yes ☐ No

If yes, please provide an email or mailing address: _____

DOCUMENTATION OF INFORMED CONSENT

You will be given a copy of this informed consent form after it has been signed and dated by you and the study staff.

Study Title: Selective Early Medical Treatment of the Patent Ductus Arteriosus in Extremely Low Gestational Age Infants: A Pilot Randomized Controlled Trial (SMART PDA Pilot Trial)

Name of Participant: _____

Participant / Parent / Substitute Decision-Maker

By signing this form, I confirm that:

□ This research study has been fully explained to me and all of my questions answered to my satisfaction

□ I understand the requirements of participating in this research study

□ I have been informed of the risks and benefits of participating in this research study

□ I have been informed of any alternatives to participating in this research study

□ I have been informed of the rights of research participants

□ I have read each page of this form

□ I authorize access to my infant's health information, and research study data as explained in this form

□ I have agreed, or agree, to allow the person I am responsible for, to participate in this research study

Your signature on the form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to allow your baby to participate as a subject. In no way does this waive your legal rights nor release the investigator(s), sponsors, or involved institution(s) from their legal and professional responsibilities.

If you have any questions at any time during or after the study about research in general you may contact the Research Office of IWK Health at (902) 470-7879, Monday to Friday between 8:00a.m. and 4:00p.m

_____	_____	_____
Name of Participant / Parent / Substitute Decision-Maker (print)	Signature	Date & Time

ASSISTANCE DECLARATION

Was the participant assisted during the consent process? ☐ Yes ☐ No

The consent form was read to the participant/substitute decision-maker, and the person signing below attests that the study was accurately explained to, and apparently understood by, the participant/substitute decision-maker. The person signing below acted as a translator for the

participant/substitute decision-maker during the consent process. He/she attests that they have accurately translated the information for the participant/substitute decision-maker, and believe that that participant/substitute decision-maker has understood the information translated.

_____	_____	_____
Name of Person Assisting (Print)	Signature	Date & Time

Person obtaining consent

By signing this form, I confirm that:

□ This study and its purpose has been explained to the participant named above

□ All questions asked by the participant have been answered

□ I will give a copy of this signed and dated document to the participant

_____	_____	_____
Name of Person Obtaining Consent (Print)	Signature	Date & Time

Appendix D. Research Team

Principal Investigator: Dr Souvik Mitra, MD, MSc, PhD, FRCPC
BC Women's Hospital, Vancouver, BC & IWK Health, Halifax, NS, Canada

Co-investigators

Dr Amish Jain	Mt Sinai Hospital, Toronto, Canada
Dr Walid El-Naggar	IWK Health, Halifax, NS, Canada
Dr Michael Castaldo	BC Women's Hospital, Vancouver, Canada
Dr Abbas Hyderi	Stollery Children's Hospital, Edmonton, Canada
Dr Audrey Hébert	Chu de Quebec, Quebec City, Canada
Dr Dany Weisz	Sunnybrook Health Sciences Centre, Toronto
Dr Jenny Koo	Sharp Mary Birch Hospital for Women and Newborns, San Diego, US
Late Dr John Cleary	CHOC Children's, Orange County, US
Dr Jon Dorling	University of Southampton, UK
Dr Patrick McNamara	University of Iowa, United States
Dr Anup Katheria	Sharp Mary Birch Hospital for Women and Newborns, San Diego, US
Dr Marjorie Makoni	OU College of Medicine, University of Oklahoma, Oklahoma City, US
Dr Lehana Thabane	McMaster University, ON, Canada
Dr Tim Disher	Eversana Inc.
Ms Fabiana Bacchini	Canadian Premature Babies' Foundation, Toronto, Canada
Dr Santokh Dhillon	IWK Health, Halifax, NS, Canada

Research Coordinators

Mr Austin Cameron, Ms Emily MacLeod, Ms Joyce Ledwidge Ms Cari-Lee Carnell, Ms Tara Hatfield	Division of Neonatal Perinatal Medicine Research Team, IWK Health, Halifax, NS, Canada

Participating sites

Site Name	Site Principal Investigator
IWK Health, Halifax, NS, Canada	Dr Walid El-Naggar
BC Women's Hospital, Vancouver, Canada	Dr Michael Castaldo
Chu de Quebec, Quebec City, Canada	Dr Audrey Hébert
Sharp Mary Birch Hospital for Women and Newborns, San Diego, US	Dr Jenny Koo
OU College of Medicine, University of Oklahoma, Oklahoma City, US	Dr Marjorie Makoni
CHOC Children's, Orange County, US	Dr John Cleary
Stollery Children's Hospital, Edmonton, Canada	Dr Abbas Hyderi, Dr Joseph Ting

Appendix E. Summary of protocol amendments and explanations

Version	Version Date	Approval Required?	Change(s)
1	September 28, 2021	Yes, attached	N/A
2	October 1, 2021	No	Suggested reporting of AEs to HC; Grammatical
3	November 12, 2021	No	Suggested reporting of AEs to HC; Grammatical
4	November 18, 2021	Yes, attached	Included reporting of AEs to HC; Grammatical
5	March 21, 2022	Yes, attached	Definitions of oliguria & severe IVH
6	March 9, 2023	Yes, attached	Echo timing; Removal of "potential" AEs (wording)
7	May 2, 2023	No, not implemented	See attached, Reporting AE's to HC, Update DSMB members, clarification of SAE communication to DSMB, change wording of protocol deviation, introduce stopping rule as per DSMB
7.1	May 2, 2023	No, not implemented	Version number change at request of Alberta site
7.2	July 19, 2023	Yes	Page 22: The following sentence was deleted in keeping with protocol changes to v7.0 and v7.1 – " in addition to reporting to the institutional research ethics committee, reports of all potential AE's will be sent to the DSMB monthly"