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.
Primary Sponsor	IWK Health Centre, Halifax, Nova Scotia
Contact for Public Queries	Dr Souvik Mitra MD, MSc, PhD, FRCPC Neonatologist, BC Women's Hospital, Vancouver, Canada Associate Professor of Pediatrics, University of British Columbia Clinician-Scientist, BC Children's Hospital Research Institute Room 1N53, 4500 Oak Street Vancouver, British Columbia, V6H 3N1 Email: souvik.mitra@cw.bc.ca ; souvik.mitra@ubc.ca
Contact for Scientific Queries	Dr Souvik Mitra MD, MSc, PhD, FRCPC Neonatologist, BC Women's Hospital, Vancouver, Canada Associate Professor of Pediatrics, University of British Columbia Clinician-Scientist, BC Children's Hospital Research Institute Room 1N53, 4500 Oak Street Vancouver, British Columbia, V6H 3N1 Email: souvik.mitra@cw.bc.ca ; souvik.mitra@ubc.ca
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

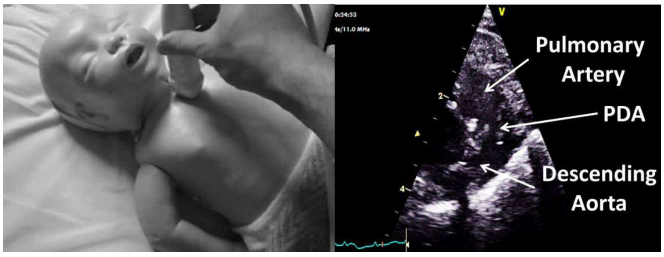
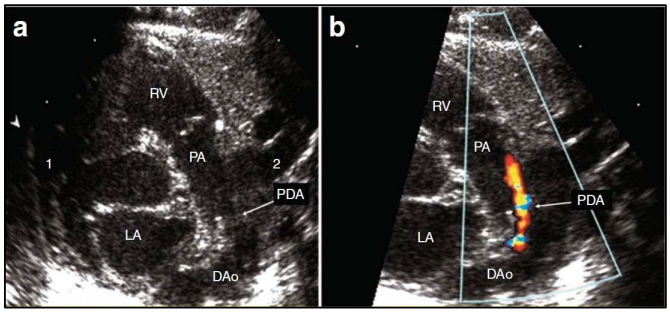
	Secondary clinical outcomes: (1) Mortality during hospital stay; (2) procedural PDA closure; (3) proportion of infants receiving any PDA pharmacotherapy; (4) proportion of infants receiving open-label rescue medical treatment; (5) CLD (defined as need for supplemental oxygen or respiratory support at 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.

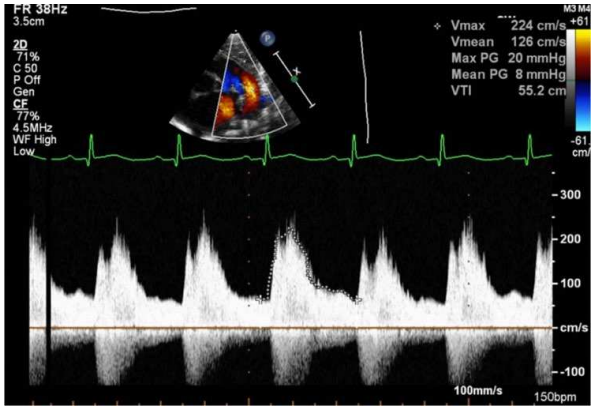
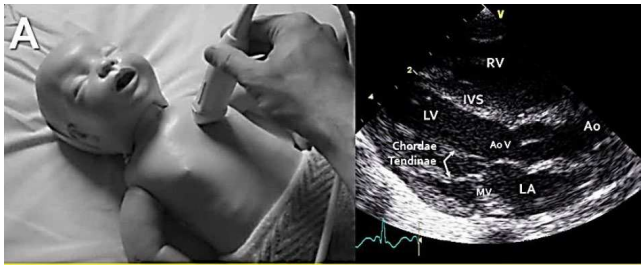
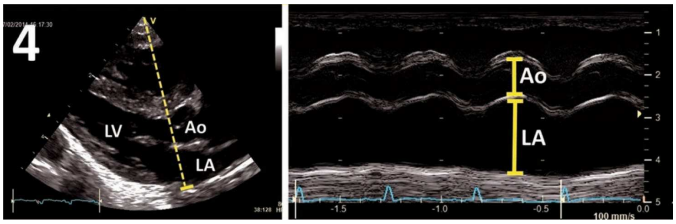
Appendix B. Standardized echocardiographic assessment of the patent ductus arteriosus (PDA)

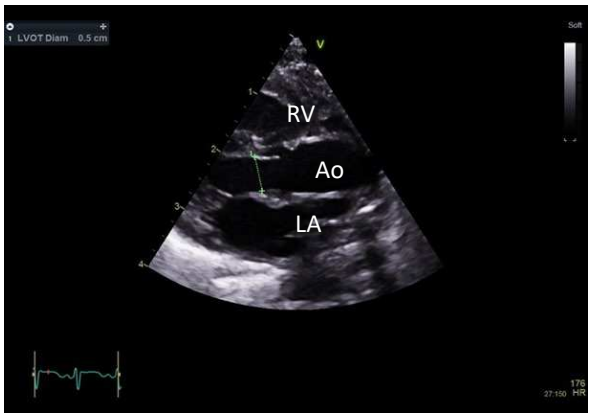
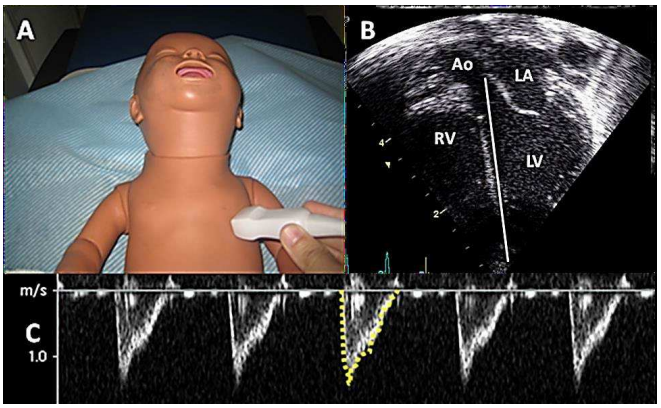
All participating centers are a part of the Neonatal Hemodynamics Research Centre (https://www.neonatalhemodynamics.com/index.html). All participating centers follow standardized protocols for echocardiographic image acquisition and measurements. These protocols have been devised following the guidelines 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).

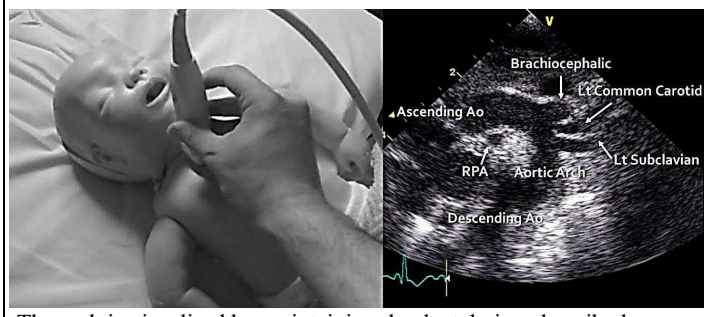
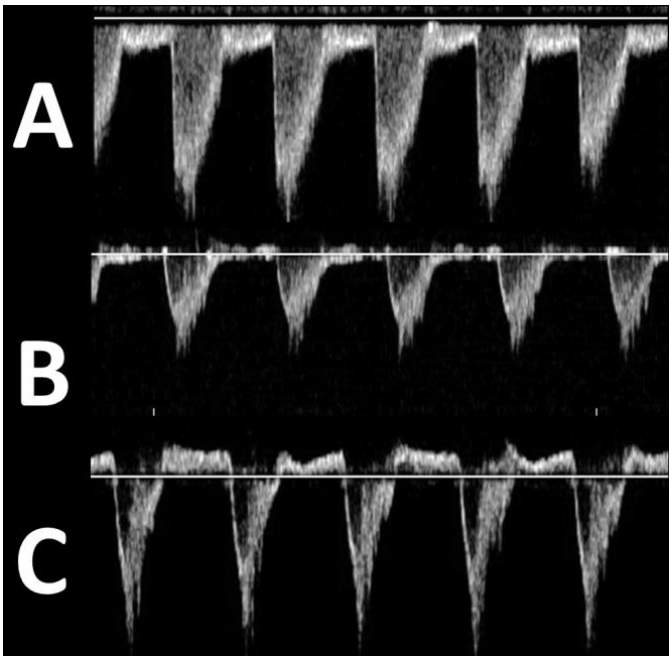
The image acquisition techniques and measurement guidelines specific to PDA assessment in this RCT are outlined as follows:

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

References

1. Mertens L, Seri I, Marek J, Arlettaz R, Barker P, McNamara P, Moon-Grady AJ, Coon PD, Noori S, Simpson J, Lai WW; Writing Group of the American Society of Echocardiography; European Association of Echocardiography; Association for European Pediatric Cardiologists. Targeted Neonatal Echocardiography in the Neonatal Intensive Care Unit: practice guidelines and recommendations for training. Writing Group of the American Society of Echocardiography (ASE) in collaboration with the European Association of Echocardiography (EAE) and the Association for European Pediatric Cardiologists (AEPC). J Am Soc Echocardiogr. 2011 Oct;24(10):1057-78
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
souvik.mitra@iwk.nshealth.ca
Division of Neonatal-Perinatal Medicine, Affiliate Scientist
IWK Health

Site Investigator: Dr. Walid El-Naggar
walid.el-naggar@iwk.nshealth.ca
902-470-7961
Division of Neonatal-Perinatal Medicine
IWK Health

Research Coordinators: Tara Hatfield & Cari-Lee Carnell
nicu.research@iwk.nshealth.ca
902-470-6630
Division of Neonatal-Perinatal Medicine
IWK Health

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"