PROTOCOL

Protocol Title: Positive End-Expiratory Pressure (PEEP) Levels during Resuscitation of Preterm Infants at Birth (The POLAR Trial).

Protocol Number: 60303

Protocol Version # and Date: Version 5.0 – Dated: 20 December 2023

REVISION CHRONOLOGY:

Version No.	Date of Change	Summary of Changes
Version 2.0	*07 August 2020*	*Inclusion of additional interim analysis and minor administrative amendments/corrections for clarification purposes.*
Version 2.1	*04 November 2020*	*Clarification of the management of participants within the Delivery Room post intervention period and minor administrative amendments/corrections for clarification purposes.*
Version 3.0	*17 February 2021*	*Addition of trial schema, further clarification relating to mandated trial procedures versus trial recommendations/guidelines and minor administrative amendments/corrections for clarification purposes.*
Version 4.0	*01 October 2021*	*Addition of information relating to the use of the Parent Education Video/Animation, alternative informed consent methods during COVID-19 and minor administrative amendments/corrections for clarification purposes.*

Version No.	Date of Change	Summary of Changes
Version 5.0	*20 December 2023*	*Removal of requirement to collect baseline medical record data from ineligible mothers, update to the Schedule of Assessments, clarifications to the Respiratory Deterioration Criteria (Table 7.1) and Criteria to Intubate (Table 7.2), addition of Secondary Endpoint, Clarification of the follow-up assessments for the trial, and minor administrative amendments throughout for clarification purposes.*

CONFIDENTIAL

STATEMENT OF COMPLIANCE

This clinical trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

This clinical trial will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national, local, and international regulations.

This clinical trial is not sponsored by any pharmaceutical company or other commercial entity.

CONTENTS

PROTOCOL SYNOPSIS

TITLE	Positive End-Expiratory Pressure Levels during Resuscitation of Preterm Infants at Birth (The POLAR Trial).
OBJECTIVES	This trial aims to establish whether the use of a high, dynamic PEEP strategy to support the lung during stabilisation at birth, compared with a static, standard PEEP strategy, increases the rate of survival without bronchopulmonary dysplasia (BPD) in extremely preterm infants born <29 weeks post-menstrual age (PMA).
DESIGN	A phase III/IV, international multicentre prospective randomised control trial to be conducted in the delivery rooms (DRs) of tertiary NICUs experienced in respiratory trials across Australian, European, , British, and North American neonatal networks.
OUTCOMES	The primary outcome is the composite outcome of either death or BPD at 36 weeks PMA as assessed by standard oxygen reduction test. The secondary outcomes include important short-term respiratory morbidity and potential harm outcomes in the DR and NICU. Principal secondary outcomes include: - Failure of non-invasive ventilation in first 72 hours - Oxygen requirement ≥50% for 3 or more consecutive hours in first 72 hours - Surfactant therapy in first 72 hours - Air leak and/or pulmonary interstitial emphysema in first 10 days of life - Patent ductus arteriosus requiring therapy - Grade 3 or 4 intraventricular haemorrhage (on ultrasound) - Intubation in the delivery room
RECRUITMENT PERIOD	Approximately 5 years after first infant randomised.
FOLLOW UP PERIOD	24 months
INTERVENTIONS	Dynamic PEEP Group: Respiratory support with a dynamic PEEP algorithm (8-12 cmH_2O) individualised to clinical need. Static PEEP Group: Respiratory support with a static PEEP (5-6 cmH_2O) consistent with current Neonatal Resuscitation Program (NRP) guidelines.
NUMBER OF PARTICIPANTS	906 participants (453 infants per group)
POPULATION	Preterm infants born between 23 weeks and 0 days and 28 weeks and 6 days PMA (post menstrual age) by best obstetric estimate who are born in participating study centres and require respiratory intervention from birth.
TRIAL REGISTRATION	Clinicaltrials.gov Registry No: NCT04372953 ANZCTR Registry No: ACTRN12618001686291

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	*TERM*
AE	*Adverse Event*
BPD	*Bronchopulmonary Dysplasia*
Bpm	*Beats per Minute*
CAPA	*Corrective and Preventative Actions*
CONSORT	*Consolidated Standards of Reporting Trials*
CEBU	*Clinical Epidemiology & Biostatistics Unit*
CI	*Confidence Interval*
cmH_20	*Centimetre of Water*
CMV	*Conventional Mechanical Ventilation*
CPAP	*Continuous Positive Airway Pressure*
CRF	*Case Report Form*
CXR	*Chest x-ray*
DCC	*Delayed umbilical Cord Clamping*
DCCe	*Data Coordinating Centre*
DMS	*Data Management System*
DR	*Delivery Room*
DSMC	*Data Safety Monitoring Committee*
ECG	*Electrocardiogram*
ETT	*Endotracheal Tube*
FiO_2	*Fraction of Inspired Oxygen*
FRC	*Functional Residual Capacity*
g	*Grams*
GA	*Gestational Age*
GDPR	*General Data Protection Regulation*
HFOV	*High-Frequency Oscillatory Ventilation*
HR	*Heart Rate*
HREC	*Human Research Ethics Committee*
ILCOR	*International Liaison Committee on Resuscitation*
IRB	*Institutional Review Board*
ITT	*Intention-To-Treat*
IVH	*Intraventricular Haemorrhage*
MCRI	*Murdoch Children's Research Institute*
MCTC	*Melbourne Children's Trial Centre*
mmHg	*Millimetre of Mercury*
MoP	*Manual of Procedures*

MRFF	*Melbourne Research Future Fund*
MR SOPA	*Abbreviation used in NRP to summarise corrective steps that may improve respiratory status: Adjust **m**ask/interface, **r**eposition head to open airway, **s**uction mouth, **o**pen mouth and lift jaw, commence inflation **p**ressure, and consider **a**rtificial airway*
NHMRC	*National Health and Medical Research Council*
NICU	*Neonatal Intensive Care Unit*
NRP	*Neonatal Resuscitation Program*
OR	*Odds Ratio*
PARCA-R	*Parent Report of Children's Abilities (PARCA)*
PCO_2	*Partial Pressure of Carbon Dioxide*
PEEP	*Positive End Expiratory Pressure*
PID	*Participant Identification Number*
PIP	*Peak Infiltrating Pressure*
PMA	*Postmenstrual Age*
PPV	*Positive Pressure Ventilation*
RCH	*Royal Children's Hospital*
RDS	*Respiratory Distress Syndrome*
REB	*Research Ethics Board*
RL	*Regional Leads*
RRR	*Relative Risk Reduction*
RWH	*Royal Women's Hospital*
s	*Seconds*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SI	*Sustained Inflation*
SIV	*Site Initiation Visit*
SoP	*Standard Operating Procedure*
SpO_2	*Saturation of Peripheral Oxygen*
SSI	*Significant Safety Issue*
TCC	*Trial Coordinating Centre*
TGA	*Therapeutic Goods Administration*
TSC	*Trial Steering Committee*
URSAE	*Unexpected and Related Serious Adverse Event*
USM	*Urgent Safety Measure*

INVESTIGATOR AGREEMENT & SIGNATURE PAGE

The Principal Investigator at each site has the overall responsibility for the conduct and administration of the trial in compliance with the protocol for which was given approval by the HREC/IRB. The Investigator(s) is responsible for ensuring the privacy, safety, and welfare of the trial participants, during and after the trial. The Principal Investigator should sign the protocol or an alternative contract to confirm agreement.

I have read the protocol entitled "**Positive End-Expiratory Pressure Levels during Resuscitation of Preterm Infants at Birth (The POLAR Trial**)."

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee (HREC) or Institutional Review Board (IRB) (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki, Good Clinical Practice guidelines (GCP) adopted by the TGA [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments] and the Sponsor's SOPs. In addition, the trial will be conducted in compliance with all applicable laws and regulatory requirements relevant to each participating country.

Changes to the protocol will only be implemented after written approval is received from the Human Research Ethics Committee (HREC) or Institutional Review Board (IRB) (as appropriate), with the exception of medical emergencies.

I will ensure that trial staff fully understand and follow the protocol and evidence of their training is documented on the trial training log. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Name (please print)	**Role/Position**	**Signature and Date**
	Site Principal Investigator	

For and on behalf of the Study Sponsor:

Name (please print)	**Role/Position**	**Signature and Date**
Prof David Tingay	Sponsor-Investigator	

1. TABLE OF PROCEDURES & STUDY SCHEMA

1.1 Table of Procedures

Procedure	Timing	Description
Eligibility Screening	Following maternal admission to labour and delivery unit, and before delivery	Maternal charts will be reviewed for prospectively eligible infant and all inclusion and exclusion criteria will be screened.
Informed Consent	Antenatally before delivery or following delivery and before hospital discharge	Informed consent will occur through a prospective or deferred method, dependent on site HREC/IRB approval.
Randomization	Immediately before birth	Infants will be randomized to receive either the Static intervention or Dynamic intervention
Pulse Oximetry Monitoring	Duration of delivery room care	Pulse oximetry monitoring of peripheral oxygen saturation (SpO_2) and heart rate are required from as soon as practical after birth. Heart rate can be monitored via ECG according to site practice.
Clinical Assessment	First 20 min from birth only	Clinical assessment of infant respiratory effort should occur by one or more members of the neonatal resuscitation team every minute (unless impractical). See Section 7.2-7.4.
Static Intervention: PEEP 5-6 cmH_2O	First 20 min from birth only	Delivery of a positive end-expiratory pressure of 5 to 6 cmH_2O via an appropriate T-piece neonatal resuscitation device (for example Neopuff) in accordance with the algorithm detailed in Section 7.3.
Dynamic Intervention: PEEP 8-12 cmH_2O range	First 20 min from birth only	Delivery of a positive end-expiratory pressure between 8 and 12 cmH_2O via an appropriate T-piece neonatal resuscitation device (for example Neopuff) in accordance with the algorithm detailed in Section 7.4.
Escalation of Respiratory Support in the Delivery Room	First 20 min from birth only	As defined in Table 7.1, if an infant demonstrates signs of respiratory deterioration (bradycardia, apnoea and/or increasing oxygen needs) a series of resuscitative measures should be implemented (broadly in accordance with the NRP 'MR SOPA'). This includes assessing facemask/interface and airway patency, providing positive pressure ventilation (PPV) and/or intubation.

Delivered Supplementary Oxygen	First 20 min from birth only	Respiratory support to commence in 30% supplementary oxygen (FiO_2 0.3) and increased in increments if the criteria for respiratory deterioration (see above; Table 7.1) are met. FiO_2 can be decreased if an infant has SpO_2 above target range.
Positive Pressure Ventilation Settings	First 20 min from birth only	If criteria to start PPV are met (Table 7.1), PPV should be commenced at 20-25 cmH_2O. Transient inflating pressures up to 35 cmH_2O are permitted if no chest wall movement at 25 cmH_2O. PPV should be delivered at a rate 40 – 60 inflations per minute.
Intubation in the Delivery Room	First 20 min from birth only	Intubation should be performed if criteria to intubate during the intervention period is met, as defined in Table 7.2
Assessment of Bronchopulmonary Dysplasia (BPD) Status	At 36 weeks post-menstrual age	BPD status will be assessed using the Modified Walsh Definition and standard oxygen reduction test at no earlier than 36 weeks post-menstrual age.
Adverse Event Monitoring	From time of birth until 48 hours after 36-week PMA BPD assessment	All randomized infants will be monitored for adverse events according to the criteria set in section [section 11.0]
Medical Record Data Collection	From time of birth until after standard of care 2-year developmental assessment	Medical records will be reviewed, and data extracted throughout the infant's hospital stay, and again following the infant's standard of care 2-year developmental assessment.

1.2 Non-Mandated Procedures

The following procedures or therapies detailed in the protocol are not mandated within the POLAR trial:

ANTENATAL CARE:

Antenatal care is at the discretion of the clinicians managing the pregnancy. The POLAR Trial does not mandate any specific antenatal care or mode of delivery.
The POLAR Trial recommends, but does not mandate, maternal corticosteroids to aid fetal lung maturation.

DELIVERY ROOM MANAGEMENT:

The POLAR Trial does not mandate delivery room management outside of the study procedures described in the table of procedures above (Table 1.1). Method and timing of umbilical cord clamping/milking, and timing, method and type of exogenous surfactant can be as per standard practice at each site.

Facial resuscitation device interface is not mandated but must be able to connect to T-piece pressure device that can deliver a settable pressure during neonatal resuscitation.

Respiratory support, including PEEP and PPV levels, after the first 20 minutes from birth can be as per standard practice at each site. To attempt to maintain commonality across sites, the POLAR Trial recommends, but does not mandate, respiratory support guidelines provided in Section 6.6.

NICU MANAGEMENT:

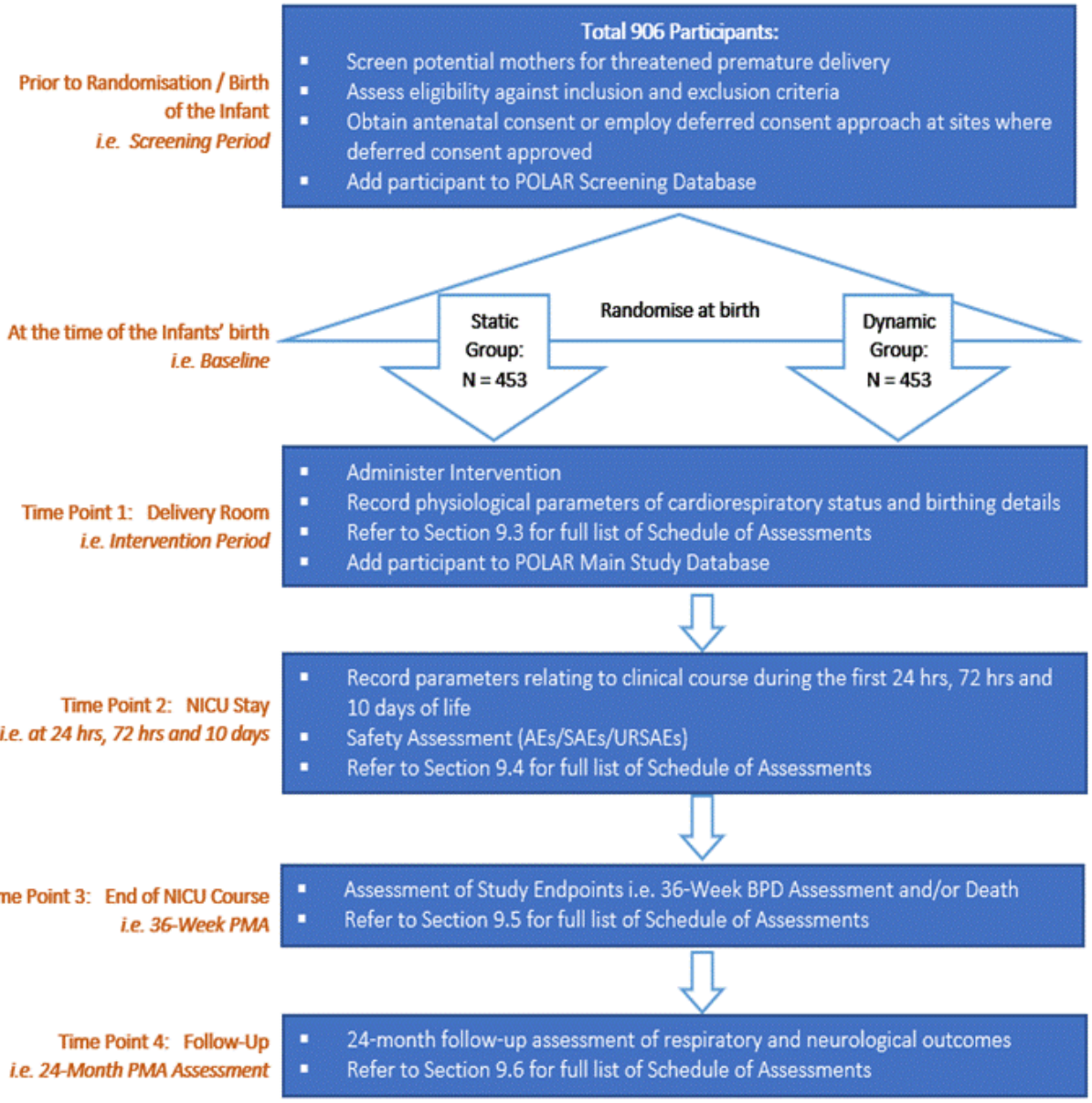
The POLAR Trial does not mandate NICU management, and clinical care will be as per standard practice at each site.

The POLAR Trial offers recommendations for NICU management in sections 7.7 and 7.8, including recommendations on criteria for PEEP management, timing, method and type of exogenous surfactant, mode, and strategy of invasive (via endotracheal tube) and non-invasive respiratory support (including high-frequency oscillatory ventilation), mode and timing of weaning from respiratory support and/or supplementary oxygen, and respiratory support after 36 weeks post-menstrual age.

POST NICU MANAGEMENT:

Post NICU management follow up and management will be as per local site practice, including routine preterm follow up programs and assessment at 24 months age.

1.3 Study Schema



2. ADMINISTRATIVE INFORMATION

2.1. Trial Registration

The Sponsor-Investigator, Prof David Tingay, is responsible for registering the trial with an appropriate clinical trial registry prior to accrual of the first trial participant. This trial is registered on www.clinicaltrials.gov (NCT04372953) and ANZCTR (ACTRN12618001686291), as per Sponsor SOP.

2.2. Sponsor

Study Sponsor	Murdoch Children's Research Institute (MCRI)
Sponsor-Investigator/ Coordinating Principal Investigator	Professor David Tingay
Email Address	david.tingay@rch.org.au / david.tingay@mcri.edu.au
Address	Flemington Road, Parkville, VIC, 3052, Australia.

On behalf of the Sponsor, MCRI, the Coordinating Principal Investigator (CPI) leading the trial will undertake and/or oversee those Sponsor responsibilities delegated by the Sponsor. Prof David is also responsible for the overall design, management and conduct of the trial and the analysis of data and decision to publish results.

2.2.1 Region Principal Investigator

The term Region Principal Investigator is used to describe the region-level Investigator (i.e., the Region Principal Investigator for sites outside of Australasia) responsible for an area including multiple sites in this multi-site international clinical trial. There are three Region Principal Investigators assuming these roles in this trial:

Name	Institute/Affiliation	Region
Prof Anton van Kaam	Amsterdam University Medical Centre	Europe
Prof Charles Roehr	National Perinatal Epidemiology Unit (NPEU) Clinical Trial Unit, University of Oxford	UK
A/Prof Elizabeth Foglia	Hospital of the University of Pennsylvania	North America

2.3. Expected Duration of Study

The study is expected to take approximately 5 years to recruit the required number of participants from the date of when the first participant is enrolled into the trial . It is anticipated that recruitment will cease mid-2026, with the last participant ceasing the two-year follow up period by mid-2028.

Participation in the study intervention phase (Static or Dynamic group) will last the duration from the time of birth until 20 minutes of life.

The entire study duration for each participant commences in the delivery room (at birth) and is completed at the 24-month PMA follow-up timepoint.

2.4. Contributorship

Name	Institute/Affiliation	Summary of Contribution
Prof David Tingay	MCRI, Royal Children's Hospital, Melb, AUS	Study Design, Author
Ms Liz Perkins	MCRI, Royal Children's Hospital, Melb, AUS	Author
Dr David Stewart	RCH, Royal Women's Hospital, Melb, AUS	Author
A/Prof Louise Owen	MCRI, Royal Women's Hospital, Melb, AUS	Study Design, Author
Dr Omar Kamlin	MCRI, Royal Women's Hospital, Melb, AUS	Study Design, Author
Ms Francesca Orsini	MCRI, Melbourne, AUS	Study Design, Author
Ms Laura Galletta	MCRI, Melbourne, AUS	Author
Prof Anton van Kaam	Amsterdam University Medical Centre, Netherlands	Study Design, Author
Prof Peter G Davis	MCRI, Royal Women's Hospital, Melb, AUS	Study Design, Author
A/Prof Elizabeth Foglia	Hospital of the University of Pennsylvania / Children's Hospital of Philadelphia, USA	Study Design, Author
Prof Helmut Hummler	Sidra Medicine, Qatar	Study Design, Author
Prof Sherry Courtney	Arkansas Medical Centre, Little Rock, USA	Study Design, Author
A/Prof Andy Gill	King Edward Memorial Hospital, Perth, AUS	Study Design, Author
Ms Danielle Weinberg	Hospital of the University of Pennsylvania, USA	Protocol Review
Ms Kayleigh Stanbury	National Perinatal Epidemiology Unit (NPEU), University of Oxford	Protocol Review
Ms Elizabeth Nuthall	National Perinatal Epidemiology Unit (NPEU), University of Oxford	Protocol Review

3. INTRODUCTION AND BACKGROUND

3.1. Background and Rationale

All infants born <29 weeks' postmenstrual age (PMA) require positive end-expiratory pressure (PEEP) at birth. PEEP is a simple, feasible and cost-effective therapy to support extremely preterm infants that is used globally. **The effective and safe level of PEEP to use after preterm birth remains the most important unanswered question in neonatal respiratory medicine.** We will undertake an international multicentre randomised controlled trial to address the following question:

In extremely preterm infants, does the use of a high, dynamic PEEP level strategy to support the lung during stabilisation ('resuscitation') at birth, compared with the current practice of a static PEEP level, reduce the rate of death or bronchopulmonary dysplasia (BPD)?

This trial will address **four key knowledge gaps** identified in the most recent 2015 International Liaison Committee of Resuscitation (ILCOR) Neonatal consensus statement [2]:

- Assessing whether **individualising (dynamic) PEEP** is superior to **static PEEP**
- The uncertainty regarding applied pressure strategies to support the lung during stabilisation at birth arising from the lack of a properly powered, well-designed randomised trial specifically addressing important outcomes for respiratory support in the Delivery Room (DR)

- The optimal PEEP strategy to use
- Determining the differential effects of PEEP at different gestational ages.

For this study, the term PEEP refers to the delivery of positive pressure (via a bias flow of gas) to the lungs during expiration by any method of assisted respiratory support, this includes:

1. Continuous Positive Applied Pressure (CPAP; a method of non-invasive respiratory support). During CPAP no other type of positive pressure is delivered as the infant supports tidal ventilation using her/his own spontaneous breathing effort. PEEP during CPAP has also been called 'continuous distending pressure.

2. Positive Pressure Ventilation (PPV). During PPV PEEP is delivered between periods of an applied inflating pressure (PIP) delivered at a clinician-determined rate. PPV can be delivered via a mask or other non-invasive interface (also termed non-invasive positive pressure ventilation; NIPPV), or via an endotracheal tube (often termed continuous mechanical ventilation; CMV).

3. High-frequency oscillatory ventilation (HFOV) or high-frequency jet ventilation. These are modes of invasive PPV in which PIP is delivered at very fast rates (>120 inflations per minute) and at very small tidal volumes. During HFOV a mean airway pressure is determined by the clinician which is equivalent to the PEEP during other modes. During high-frequency jet ventilation the clinician sets a PEEP similar to CMV.

As all of these modes of ventilation have a similar goal of applying a pressure to the lung during expiration (usually to prevent lung collapse) the term PEEP has the same physiological result despite different methods of application.

Non-Invasive Ventilation and PEEP: The foundations of neonatal lung protective ventilation:

Extremely preterm birth (<29 weeks PMA) exposes the lung to ventilation before sufficient alveolarisation and are frequently surfactant deficient [3]. This is known as respiratory distress syndrome (RDS). RDS causes lung injury and predisposes survivors of preterm birth to chronic lung disease of prematurity, known as bronchopulmonary dysplasia (BPD). Prematurity is associated with life-long adverse effects. However, BPD further increases the risk of poor neurodevelopmental outcomes and impaired lung function into adulthood. BPD affects 50-60% of infants born <29 weeks PMA [4]. More than 2000 infants are born extremely preterm annually in Australia, making preterm birth and associated BPD a growing public health concern [5, 6]. It is now established that RDS-mediated lung injury begins at birth, and once initiated is potentiated by ongoing respiratory support [7]. Any reduction in the global burden of preterm lung disease requires development of **lung protective ventilation strategies** that begin in the Delivery Room when air-breathing first begins.

Almost all infants born extremely preterm will require some respiratory support to support the respiratory transition and in the first hours of life. In the modern era, respiratory support is a major contributor to the development of BPD [3]. It creates injurious lung volume states (atelectasis and over-distension) and secondary inflammatory mechanisms (shear force injury, oxygen toxicity and biotrauma). This understanding of pathophysiology has led to the development of strategies to achieve gas exchange whilst avoiding injurious consequences of respiratory support from the first breath. Such strategies are collectively known as *lung protective ventilation [3, 8].* Despite this more sophisticated understanding of respiratory support, clinical trials of many of these strategies have not led to large reductions in BPD. A criticism of many of these trials has been:

1. A lack of guidance on optimal application of the ventilation modality in question, and
2. Limiting the intervention to the Neonatal Intensive Care Unit (NICU), well after the sequence of lung injury has begun in the first 'golden hour' of life.

Currently, there are no new modes of respiratory support that offer promise of significantly reducing preterm lung injury. Rather, improvements are possible if we can optimally apply existing therapies. Our study represents a paradigm shift in neonatal lung protective trials, as it focuses not on a specific modality, but on individualising an aspect of lung protective ventilation that is common to all respiratory modalities to optimise benefit; positive end expiratory pressure (PEEP). The lung protection conferred by individualised PEEP has been demonstrated in animal models [9-13], observational neonatal studies[14-16] and large adult human randomised control trials [17, 18]. It has been poorly studied in newborns.

PEEP refers to any positive pressure applied to the lung during expiration to overcome the resultant lung collapse (atelectasis) associated with expiration. **PEEP can be delivered during any mode of non-invasive and invasive (via an endotracheal tube) support.** PEEP is particularly relevant in the surfactant-deficient preterm lung with RDS. As lung collapse is the functional hallmark of RDS, PEEP remains the only respiratory support parameter that is consistently lung protective in both preclinical and clinical preterm studies[19]. No other aspect of respiratory support has demonstrated lung protection in the absence of PEEP. It has been repeatedly shown that lung volume is directly related to the level of PEEP[3, 10]. Surfactant-deficient RDS is a problem of poor respiratory system compliance leading to lung collapse (atelectasis). Atelectasis manifests when end expiratory pressure (both applied and spontaneously generated) is insufficient. Applied correctly, PEEP stabilises functional residual capacity (FRC), reversing or preventing atelectasis, improves surfactant function and ventilation efficacy and increases intrinsic respiratory drive. Through these mechanisms, optimal PEEP can help avoid unnecessary intubations, which further reduces BPD risk. PEEP is also the only respiratory support parameter a clinician can alter during *continuous positive airway pressure* (CPAP), the most commonly used non-invasive mode of respiratory support for preterm infants for respiratory care early after birth in the Delivery Room. Meta-analysis of existing trial data shows that early CPAP reduces death or BPD compared to intubation and mechanical support in preterm infants; RR 0.89 (0.79, 0.99) [20]. For most preterm infants' non-invasive modalities are now the primary means of respiratory support [5, 21].

What PEEP? The optimal level of PEEP during preterm lung disease remains controversial:

Although current recommendations for preterm infants stipulate that any type of respiratory support for RDS includes PEEP from birth, **this practice has arisen without specific trial evidence to guide its application.** Preclinical studies have repeatedly demonstrated that a 'high' PEEP is needed to reverse atelectasis and reduce injury[19]. Worldwide, the definition of 'high' PEEP varies considerably, PEEP levels of 5-8 cmH_2O are most commonly used, but a range of 3-15 cmH_2O are frequently reported [21-24]. This wide variation may have confounded many preterm lung protective trials, especially those comparing CPAP with invasive (via an endotracheal tube) support [3].

The wide variation in PEEP practices means that it is difficult to define 'high' PEEP [23]. What one clinician considers a high PEEP maybe considered normal or low by another. Rather than focusing on clinician-defined PEEP levels it is more appropriate to consider whether the PEEP 'dose' is adequate to treat the individual respiratory problem. Worse atelectasis requires a higher PEEP. We, and others, have shown that 7-10cmH_2O PEEP corrects atelectasis, creates less injurious breathing patterns and results in less need for intubation than 4-6cmH_2O PEEP in preterm infants in the NICU [24, 25]. However, **prolonged use of PEEP** >10cmH_2O impairs work of breathing and may increase the risk of air leak (e.g., pneumothorax)[26]. The degree of atelectasis differs in each baby, and also changes with disease progression. **Thus, a single PEEP value cannot be assumed to be appropriate, or safe, for all infants at all times**. A more physiological approach is to define appropriate PEEP by the severity of lung disease and consequent pressure needs at that time; high PEEP during atelectasis, then reduced to minimise harm once lung aeration has been established. From these principles, the **concept of dynamic PEEP** has arisen.

Dynamic PEEP: A Novel Method of Individualising PEEP Levels:

Most Neonatal Intensive Care Units (NICU) use a static narrow range of PEEP settings[22]. Arguably, a more appropriate approach is to ask *what PEEP does this individual infant need right now.*

The most recent 2019 European consensus on RDS recommends that PEEP should be titrated to individual needs in preterm infants during conventional ventilation but provides no guidance on how to do so[27]. Work in this area is based on a large body of preclinical and observational studies demonstrating that delivering a PEEP titrated to the pathophysiological needs of the lung (***dynamic PEEP***) reduces lung injury and improves short term outcomes [11-13]. These studies have used a rapid stepwise increase in PEEP, to the level needed to reverse atelectasis in that patient. Once there is confirmation of clinical improvement, PEEP is quickly reduced to avoid the risks of over-distension [3, 14-16]. The use of an initial high PEEP level is also one of the factors attributed to the reduced rates of death/BPD in a large trial of high-frequency ventilation for preterm infants [28] compared with other similarly sized trials [29]. Trials of dynamic PEEP in adults with acute respiratory distress syndrome suggest that it is most likely to be effective when applied in early disease, in patients without shock and in fluid-filled but surfactant deficient lungs[18]; a condition very similar to the preterm lung at birth.

The Transition to Air-Breathing at Birth is a Rapidly Changing Event Reliant on Sufficient PEEP:

The majority of very preterm infants need respiratory support in the Delivery Room. Birth poses three challenges to the establishment of an adequate functional residual capacity (FRC)[30]. These are:

1. The need to transition from a fluid-filled to aerated state,
2. The need to prevent lung fluid influx back into the alveolar spaces; and
3. The need to defend that FRC against RDS-mediated atelectasis.

In preclinical studies we, and others, have shown that PEEP is required to establish adequate FRC with the very first lung inflations at birth and to reduce the molecular events that cause lung injury [7, 10, 31]. Furthermore, the initial PEEP needed to establish FRC in the fluid-filled lung is higher than the PEEP needed to prevent RDS-mediated atelectasis in aerated lungs [10].

How Best to Support the Preterm Lung as it Transitions to Air-Breathing at Birth:

There are currently two approaches to supporting the preterm lung during transition from a fluid-filled to aerated state, and then maintaining FRC during tidal breathing. One is the standard Neonatal Resuscitation Program (NRP), which uses a static 5-7cmH_2O PEEP to support tidal ventilation[32]. The other approach is to use an initial high pressure to intentionally facilitate lung fluid clearance. Preclinical studies demonstrated faster aeration when a sustained inflation (SI) was used[30]. Recently, human studies of one or two high-pressure SIs to aid lung aeration prior to the NRP approach have been conducted [33]. In a single centre study, te Pas reported a reduced need for intubation in the first 72 hours (OR 0.57 [95% CI 0.32-0.98]) and less BPD at 36 weeks PMA (OR 0.41 [0.18-0.96]) in 217 preterm infants randomised to an initial SI plus NRP (6cmH_2O PEEP) compared with no PEEP or SI [34].

Recently a moderately large trial led by Kirpalani, Keszler, Davis (Trial Investigators on POLAR) and others compared SI against NRP in infants 23-26 weeks' PMA; The NICHD-funded Sustained Aeration of Infant Lungs (SAIL) Trial [33]. This trial was ceased in Jan 2018 (440 of 600 recruited) due to higher mortality in the first 2 days of life attributed to the SI. The SAIL Trial findings raise concerns about the safety of SI and re-focuses clinical interest on methods of using PEEP to optimise lung aeration in an individualised fashion immediately after birth.

PEEP levels used in DR research and clinical practice vary widely, with PEEP settings between 5-8 cmH_2O being used in previous DR trials [26, 35, 36]. With new, simple devices to deliver pressure in the DR, clinicians increasingly seek to determine *how best to manage PEEP in the DR?* At birth, the pressure needs of the lung are unknown and change rapidly during respiratory transition [10]. It is in this state of uncertainty that dynamic PEEP offers the promise of improved outcomes.

2.2.2 Pilot Data to Support a Dynamic PEEP Strategy in the Delivery Room

We have demonstrated that dynamic PEEP strategies are feasible and improve short-term outcomes in intubated preterm infants in early life [14, 16]. Difficulties in reliably delivering a consistent PEEP during CPAP (due to variable mouth/interface leak and the contribution of spontaneous breathing) have been considered a hindrance to individualising PEEP levels. We demonstrated that this is not the case. We assessed a dynamic PEEP strategy in 20 preterm infants <32 weeks' PMA and <18 hours old managed solely with CPAP from birth [37]. In this study both FRC and transpulmonary pressure were measured as PEEP was increased in steps from 5-6 (clinical use), to 8 and then 10 cmH_2O (Figure 1). PEEP 10 cmH_2O was needed to reverse atelectasis, without over-distension.

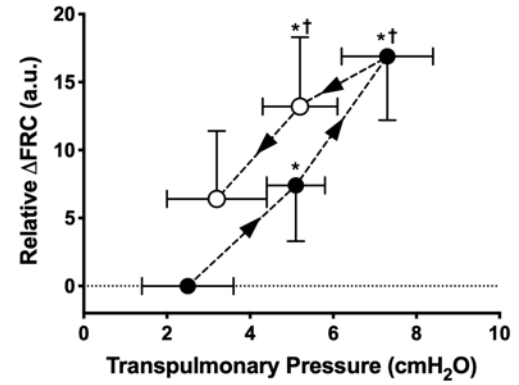


Figure 1. Dynamic PEEP strategy (5 to 8 to 10 to 8 to 6 cmH_2O) improves functional residual capacity (FRC) in preterm infants. *p<0.05 vs 5 cmH_2O PEEP, † vs initial 8 cmH_2O.

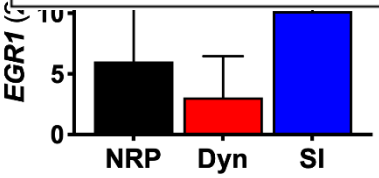


Figure 2. Reduced expression of EGR1 (a mRNA marker of early lung injury) in 125d preterm lambs (n=86) using a Dynamic PEEP strategy compared to the Neonatal Resuscitation Program static PEEP approach and a sustained inflation (SI). *p<0.05 (Tingay et al *AJRCCM* 2019).

Importantly, the volume gains at 10 cmH_2O were maintained when PEEP was then decreased to 8 cmH_2O in 65% of infants. The higher PEEP levels improved ventilation efficiency and were well tolerated without air leaks.

These data provide the first evidence that a dynamic approach to PEEP can alter lung volume during CPAP in very early life. It also demonstrates physiological demarcation between a PEEP of 5-6cmH_2O and 8-10cmH_2O.

3.1.1.2 Dynamic PEEP Approach at Birth improves Outcomes: Preclinical Evidence

Based on our prior experiences with dynamic PEEP in the NICU [14, 16], we developed a dynamic PEEP strategy to support the lung at birth [11]. We have systematically evaluated this technique in a series of 10 preclinical studies involving 250 preterm lambs at the MCRI Large Animal Facility.

These studies repeatedly demonstrated that a transient application (60-120s) of high PEEP (maximum 14-20 cmH_2O) at birth, followed by a rapid reduction to 8 cmH_2O resulted in better lung mechanics, gas exchange, improved surfactant function and reduced lung injury than either SI or static PEEP of 8 cmH_2O (analogous to the two strategies in the SAIL Trial; Figure 2) [10, 11]. Rates of air leak were also lower in the dynamic PEEP group. This work was highlighted in the most recent ILCOR guidelines as a translational priority.

2.2.3 Observational Data of Dynamic PEEP in the DR

A recent single centre report of 59 infants <29 weeks PMA managed in the first 10 min of life with an individualised lung recruitment strategy that included 5-8-10-12-15 cmH_2O PEEP steps and then gradual PEEP reduction found less need for mechanical ventilation in the first 72 hours of life (71%) compared to the NRP approach (91%). The rate of physiological BPD was also lower in the dynamic PEEP group (8.5% vs 20%). There was no difference in air leak (2% vs 1.7%)[38]. Martherus also recently observed less supplementary oxygen needs in the DR, and reduced need for intubation in the first 72 hours (26% vs 56%) using an escalating high (12-35 cmH_2O), but not de-escalating, PEEP strategy (n=27) compared with PEEP 5-8 cmH_2O (n=27) infants <29 weeks PMA[39]. However, rates of air leak were significantly higher in the high PEEP group (19% vs 4%). These findings highlight the likely benefits of transient high PEEP critical to our dynamic PEEP strategy and suggest that PEEP levels of 12 cmH_2O or less are likely to be safe.

2.2.4 Ability to Rapidly and Accurately alter PEEP Levels in the DR: Simulation Data

In the DR, PEEP is delivered via a positive pressure and flow resuscitation device (T-piece), such as the Neopuff™ Infant Resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand). A clinician manually sets the PEEP level (prior to an infant's birth) on the resuscitation device, by adjusting a small dial at the airway opening, and confirming the level visually using a manometer. Changing levels quickly is thus simple and accurate but needs to occur during a busy period of clinical care with rapidly changing conditions.

Protocol compliance with both absolute PEEP levels and also the timing of changes in PEEP will be essential to the success of our study. Furthermore, an implementation risk also arises from reduced treatment separation due to variable leak from the facemask. During neonatal resuscitation simulation training, neonatal doctors in training (n=10) all complied with the allocated trial algorithm; requiring 2.6-6.0s to change PEEP based on clinical feedback. There was no difference in mask leak at different PEEP levels, with appropriate treatment separation when comparing 5-6 with 8 cmH_2O (mean ± SD 2.8 ± 0.1 cmH_2O) and 8 with 10 cmH_2O (2.2 ± 0.2 cmH_2O).

3.2. Summary

A fundamental part of lung protective ventilation is to minimise the harmful effects of respiratory support, for example by using non-invasive respiratory support[20]. Yet, despite sophisticated approaches to respiratory support based on sound physiology, clinical trials have not shown large reductions in BPD compared with conventional care [26, 36]. A criticism of many of these trials has been:

1. A lack of guidance on optimal application of the modality in question, and
2. Limiting the intervention to the NICU, well after the initiation of the lung injury cascade has been begun in the first 'golden hour' of life [7, 31].

It is unlikely that any new mode of respiratory support will significantly reduce preterm lung injury. Rather, benefit will occur from identifying how to optimally apply existing therapies. Our study represents a paradigm shift in neonatal lung protection trials, as it focuses not on a specific modality, but on **individualising** an essential component of lung protective support (PEEP), to optimise benefit. The lung protection conferred by individualised appropriate PEEP has been demonstrated in animal models[10, 11], observational neonatal studies[14, 16, 37] and large adult randomised control trials[17]. Yet it has been poorly studied in newborns.

The POLAR trial is opportune and timely, addresses the knowledge gaps identified by ILCOR, and has scientific imperative. Our experiences with dynamic PEEP strategies provide a meaningful solution to the problem of how to best to support the preterm lung at birth compared with existing strategies (Table 1.1). Importantly, the trial is feasible, employing a technique that is already familiar to clinicians and applicable in any DR.

Table 1: Mode of Action of Different Strategies on the Respiratory Transition at Birth

Physiological Process	Static PEEP (NRP)	SI (SAIL protocol)	Dynamic PEEP
Lung Aeration	Tidal Inflations	**1-2 x 15s, 20-25 cmH_2O SI**	Tidal Inflations
Preventing lung fluid influx	Reliant on set PEEP	As per NRP	**Increasing** PEEP
Preventing atelectasis	Reliant on set PEEP	As per NRP	**Increasing** PEEP
Lung recruitment during stabilisation	Passive throughout	Passive after SI	**Active and targeted**

3.3. Study Aims

The specific trial aim is to establish whether the use of a high, dynamic 8-12 cmH_2O PEEP level strategy to support the lung during stabilisation at birth, compared with a static 5-6 cmH_2O PEEP level strategy, increases the rate of survival without bronchopulmonary dysplasia (BPD) in extremely preterm infants born <29 weeks' PMA, and reduces rates of common neonatal morbidities.

3.4. Hypothesis

We hypothesise that in preterm infants born <29 weeks PMA who receive respiratory support during stabilisation at birth, a high, dynamic PEEP strategy (i.e., PEEP 8-12 cmH_2O **individualised** to clinical need) as compared to a static PEEP of 5-6 cmH_2O, will:

1. Increase survival without BPD (primary outcome); and
2. Reduce rates of common neonatal morbidities such as failure of non-invasive respiratory support in the first 72 hours of life (secondary outcome).

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is to evaluate the impact of dynamic PEEP on the incidence of survival without BPD in extremely preterm infants born <29 weeks PMA compared with static PEEP.

4.2 Secondary Objectives

The secondary objectives of this study are to compare between groups the rates of common neonatal morbidities. We will capture many of the same initial DR resuscitation details, short-term respiratory morbidity, and potential harm secondary outcomes as the SAIL Trial[33], plus the additional secondary outcomes specific to applied positive pressures in the DR and NICU as detailed in Section 10.2. In particular, the principal secondary outcomes of:

- Individual components of primary outcome (death or BPD) at 36-weeks corrected PMA
- Failure of non-invasive ventilation in first 72 hours
- Death in the first 10 days of life
- Oxygen requirement ≥50% for 3 or more consecutive hours in first 72 hours
- Surfactant therapy in the first 7 days
- Air leak and/or pulmonary interstitial emphysema (defined on chest radiograph; CXR or lung ultrasound) in the first 10 days of life
- Patent ductus arteriosus requiring therapy in the first 72 hours
- Intraventricular haemorrhage (grade 3 and 4) (defined via imaging) by day 10 of life
- Intubation during the intervention period (up to the first 20 minutes after commencing respiratory support following birth)
- Meeting the protocol criteria for failure of non-invasive ventilation during the intervention period (up to the first 20 minutes after commencing respiratory support following birth)
- Grade of BPD[45]

The principal secondary outcomes are based on the potential risks attributed to PEEP, or on meaningful short-term respiratory benefits that can be controlled and that would justify a change in practice, even if a difference in BPD was not identified. Of these, the use of *invasive ventilation in the first 72 hours* is most strongly linked to BPD and the most common in-hospital primary outcome of DR trials [40].

In addition, long term secondary outcomes available from standard of care preterm follow-up programs and standard of care parental questionnaires will be collected at 24 months to identify:

- Cognitive delay

- Cerebral palsy
- Deafness or blindness
- Respiratory outcomes
- Death

5 STUDY DESIGN

5.1 Type of Study

This is a phase III/IV, two parallel group, non-blinded, 1:1 randomised controlled, multi-national, multi-centre, trial comparing dynamic PEEP **(dynamic group)** with standard PEEP strategy **(static group).**

The intervention will take place in the Delivery Room. The intervention period will be from the time of birth until 20 minutes after birth.

The follow-up period will extend to 36 weeks PMA (primary endpoint), and 24 months corrected GA to determine important long-term neurodevelopmental and respiratory outcomes routinely collected as part of standard neonatal follow up, such as cognitive delay, cerebral palsy, deafness, or blindness (detailed in Section 10.2)[41].

The clinical team within the DR managing enrolled and randomised infants **will not** be masked/blinded to the intervention. Clinicians need to be able to see the PEEP delivery device to assess efficacy of pressure delivery. The Research Coordinator/Study team at site will also **not** be masked/blinded to the intervention, as they will be entering trial data into the POLAR REDCap Data Management System (DMS), hence, will have access to information regarding what intervention was delivered.

Research staff based at the central Trial Coordinating Centre (TCC), the Data Coordinating Centre (DCCe) and the trial statistician will be blinded to assigned treatment.

5.2 Study Setting

The DR and NICU of tertiary perinatal centres in Australia, Europe, the UK, and North America who deliver infants born <29 weeks PMA and have an established research culture and infrastructure.

6 PARTICIPANTS AND RECRUITMENT

6.1 Number of Participants and Estimated Recruitment Timelines

There will be a total of 906 infants recruited (453 in the Dynamic group, 453 in the Static group).

We anticipate opening 25-30 recruitment centres across Australia, Europe, the United Kingdom, and North America.

It is estimated that recruitment will take approximately 5 years from the date of when the first participant is enrolled into the trial. It is anticipated that recruitment will cease mid-2026, with the last participant ceasing the follow up period by mid-2028.

The study will have Regional Leads (RLs) established in Australia ((The Murdoch Children's Research Institute/Royal Women's Hospital, Melbourne, AUS), Europe (The Amsterdam University Medical Centre, Netherlands EU), North America (The Hospital of the University of Pennsylvania, Pennsylvania USA) and the United Kingdom (University of Oxford, National Perinatal Epidemiological Unit (NPEU) Clinical Trials Unit, Oxford UK).

6.2 Eligibility Criteria

Only infants who are born in participating NICUs and deemed at birth to be eligible will be randomised into the study. Infants will be assigned to a randomised study group only if they meet all the inclusion criteria and none of the exclusion criteria.

6.2.1 Inclusion Criteria

Each infant must meet all the following criteria to be enrolled in this study:

1. The infant is born between 23 weeks 0 days and 28 weeks 6 days PMA (by best obstetric estimate)
2. Is planned to receive respiratory intervention (resuscitation) at birth with CPAP and/or positive pressure ventilation in the DR to support transition and/or respiratory failure related to prematurity
3. The infant has a parent or other legally acceptable representative[i] capable of understanding the informed consent document and providing consent on the participant's behalf either prospectively or after birth and randomisation if prenatal consent was not possible (at sites where the Ethics Committee permits waiver of prospective consent).

6.2.2 Exclusion Criteria

Infants meeting any of the following criteria will be excluded from the study:

1. The infant is not planned for active care based on assessment of the attending clinician or family decision
2. The infant has anticipated severe pulmonary hypoplasia due to rupture of membranes <22 weeks' with anhydramnios or fetal hydrops
3. The infant has a major congenital anomaly or anticipated alternative cause for respiratory failure
4. Refusal of informed consent by their legally acceptable representative
5. The infant does not have a guardian who can provide informed consent.

6.3 Recruitment, Identification and Screening of Potential Participants

Screening will occur prior to an infant's birth. The clinical team member or participating sites research coordinator will evaluate maternal admissions to the Labour and Delivery Unit at the clinical site to preliminarily assess eligibility based on estimated gestational age and maternal labour status. Mothers of potentially eligible infants may also be identified at a prenatal visit if it is deemed there is a potential risk for their baby to be born prematurely. Depending on the clinical site's consent approach, these women may be asked to consent for the trial at the prenatal visit.

All admissions for threatened premature delivery will be screened daily to ensure that eligible participants can be enrolled. The clinical team member or research coordinator will review the medical history to determine eligibility based on inclusion/exclusion criteria. The research coordinator, trained staff member or appropriately trained clinical team member will explain the study after determining eligibility. If it is practical to do so (or in centres only allowing prospective antenatal consent) they will then explain the study to eligible mothers/parents. The initial step after screening is to obtain and document informed consent. The clinical team member or research coordinator at each site will

[i] The term 'parent' will be used for the remainder of the proposal to include a parent or other legally acceptable representative

maintain a screening log of all screened mothers-infants indicating who is eligible and who is not, and of eligible mothers who have consented to the study and who has refused study participation.

6.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the trial but are not subsequently randomised to receive the study intervention or entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography (i.e., mother's year of birth only), screen failure details, and eligibility criteria.

6.4 Consent

Each clinical site is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Human Research Ethics Committee (HREC)/Institution Review Board (IRB). The approach used for obtaining informed consent (antenatal or deferred consent) for the POLAR Trial, as well as the informed consent/patient information document used by the clinical site, must be approved by the local Human Research Ethics Committee (HREC)/Institutional Review Board (IRB) before the start of the study.

Informed consent will be obtained in one of two methods depending on local requirement, either antenatal (prospective) consent approach or deferred (retrospective) consent approach (Figure 3). Antenatal (prospective) consent is the preferred method of consent for the POLAR Trial (see 6.4.2).

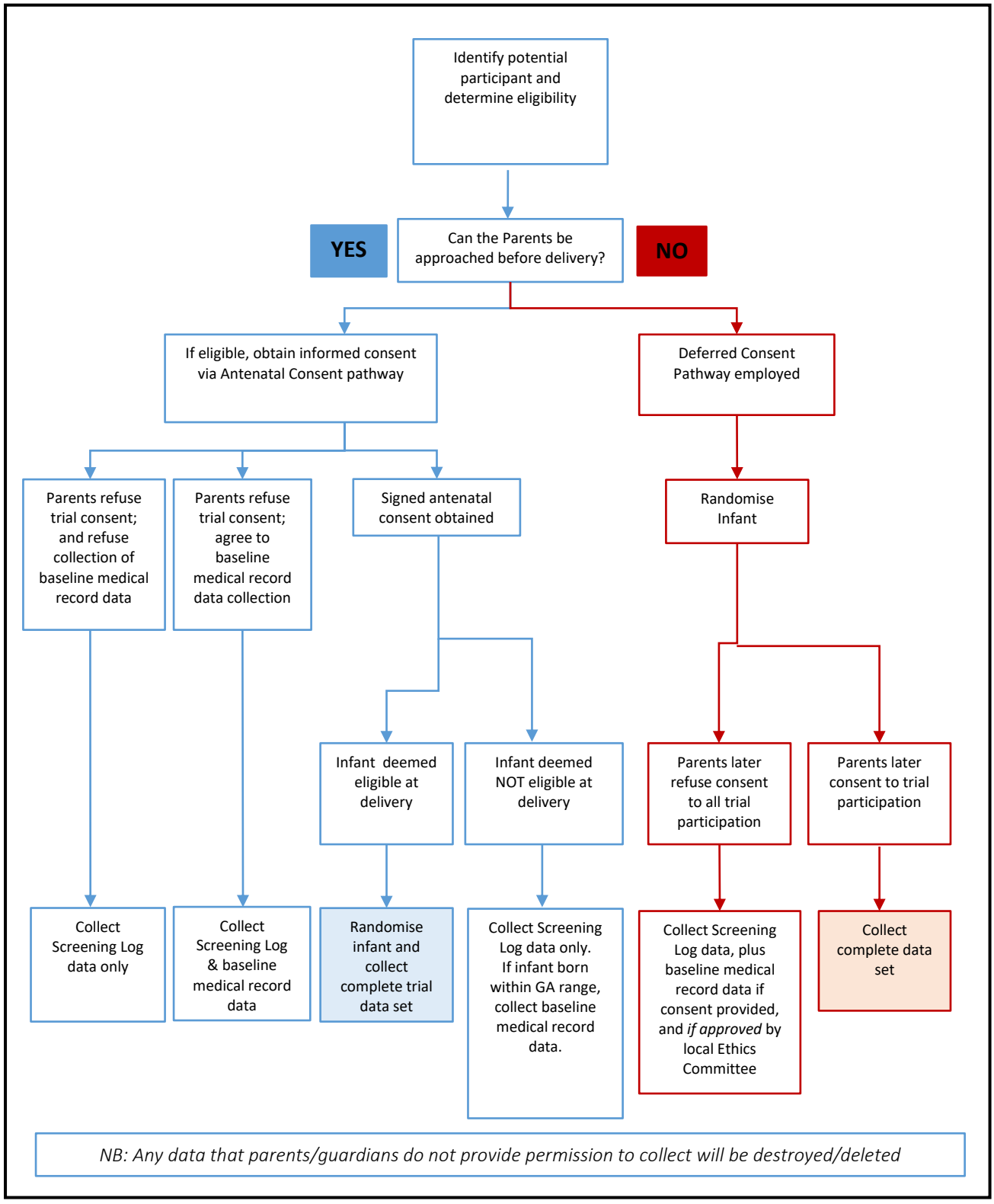
During the consent procedures, the study team members will follow the fundamental conditions for a valid informed consent:

- Disclosure of relevant information to prospective research participants and/or their legally acceptable representatives
- Comprehension of the information provided
- Voluntary agreement of the participant, free from coercion.

When all the inclusion/exclusion criteria have been addressed and the eligibility of the participant confirmed, the participant may be assigned to the randomisation group in the study.

Number of eligible participants who decline to participate in the study, as well as ineligible participants, will be recorded so that a log can be maintained of all participants screened but not enrolled. No information will be recorded on ineligible participants, other than the fact they were screened. Refer to the POLAR Manual of Procedures (MoP) for further details on recording Screening information.

Figure 3. Flow Diagram of the Consent Process (see Section 9.0 for details on the data collection)



6.4.1 POLAR Parent Educational Video/Animation

Participating sites may wish to use the POLAR parent educational video/animation generated to supplement the informed consent conversation when approaching potential parents and families about

the trial, and/or as a general reference for parents at a later time. This visual aid can be used to supplement the provision of information to parents in a non-coercive layman way, and should in no way, be used in place of a full informed consent conversation which must be held with all participants.

The parent educational videos are available in English, Spanish, Italian, French and Polish. Additional languages may be developed over time as required.

Prior to using any of the parent educational videos, each participating centre must obtain approval by their local Human Research Ethics Committee (HREC)/Institutional Review Board (IRB) prior to its use.

The videos can be accessed via the POLAR website (www.POLARTrial.org.au) and/or via a QR code for ease of accessibility. The QR code is only to be used to access the parent education video and not for publicly promoting or advertising the trial.

Refer to the POLAR Manual of Procedures (MoP) document for further information.

6.4.2 Antenatal Consent Approach

Parents will be approached for informed consent to enrol their infant into the study prior to the infant's delivery. Informed written parental consent will be obtained in the prenatal period from parents of potentially eligible infants presenting with threatened preterm delivery within the inclusion gestations.

The Infant(s) whose parents refuse to sign informed consent will not be randomised into the study.

If consent for study participation/infant resuscitation is not given, the mother may be asked to give her written consent to allow data related to the management in the delivery room, and relevant antepartum history, to be collected. The consent for baseline medical record data (i.e., delivery room data) will be restricted to only the specific medical record data collected for the POLAR Trial. The request for consent to collect only medical record data can be made after delivery. The request for consent to collect only medical record data is distinct from the Deferred Consent approach (see Section 6.4.3).

Participating sites must ensure they have local procedures and mechanisms in place to ensure that prospective participants approached in the antenatal setting who subsequently decline study participation and are then discharged home, are **not enrolled via the deferred consent pathway** should they present again precipitously.

6.4.3 Waiver of Prospective (Deferred) Consent Approach

At sites where the Human Research Ethics Committee (HREC)/Institutional Review Board (IRB) permits waiver of prospective consent (or deferred consent) to be used, eligible participants will be randomised at birth if antenatal consent was not possible, and resuscitation delivered as per allocated study group.

A clinical care team member or appropriately trained member of the research team will approach the infant's parents to obtain informed consent for continued study participation and data collection. The time of approach should be as soon as possible after delivery but, typically by day 10. If a waiver of prospective consent approach is employed, and the parent/guardian has refused to consent to ongoing participation in the trial, the site may be able to collect baseline medical record data (i.e., delivery room data) only, provided:

1. Parental permission/consent is given for collection of such data; and
2. The HREC/IRB has approved this data collection.

The infant will not be included in the study.

The wavier of prospective consent approach will only be used if antenatal consent was not possible, and this approach has been approved, in advance, by the local HREC/IRB and indicated as such in the

HREC/IRB approval documentation. At sites that do not allow waiver of prospective consent, and subsequently do not provide the necessary approvals in advance, infants must not be randomised into the study if the parents are unable to be approached before the birth.

6.4.3.1 Use of Data when Deferred Consent Decline

In situations where deferred consent was employed, and subsequently deferred consent was declined by parents/guardians, any data that may have been collected will be deleted from the trial databases, **excluding** data on any Serious Adverse Events (SAEs) participants may have experienced from the time of birth. It is important that any true safety signal is identified in the study.

If an SAE occurs within the SAE reporting timeframe, and before deferred consent has been obtained, and subsequently consent is refused or cannot be obtained from parents/guardians (for example family is lost to follow up before approached for consent), the SAE must still be reported to the Sponsor in accordance with Section 11 below.

SAE data will be assessed by the POLAR Medical Monitors as per Section 11 below and any data relevant to the SAE will **be de-identified** and only included in total aggregate data reports (Refer to Figure 4 for flow of SAE data).

These **de-identified** data will also be made available to the DSMC, to assess if a suspected safety signal of concern has occurred. These data will not be used in analysis or reporting of the primary or secondary outcomes at the time of final analysis.

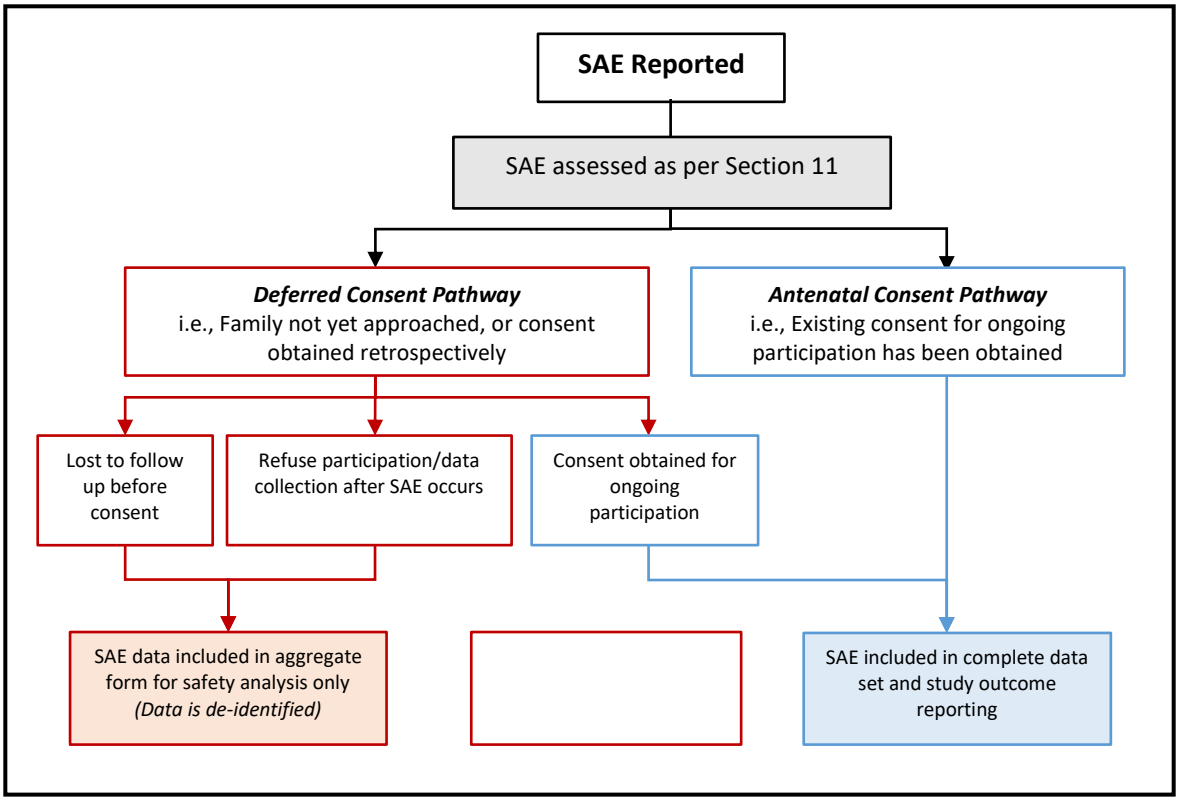
6.4.4 Alternative Consent Methods during COVID-19

At participating sites where the local Human Research Ethics Committee (HREC)/Institutional Review Board (IRB) permits alternative methods to delivering the informed consent conversation during COVID-19 restrictions, the following general principals must be applied in order to deliver the informed consent conversation with potential participants:

- The informed consent conversation may occur via telephone, the participating sites preferred Telehealth Service Provider, or a digital videoconference platform as approved by the sites HREC/IRB and its own internal organisational policies and procedures (for example Microsoft Teams, Zoom, FaceTime)
- Participants must have first provided verbal permission to be approached about the trial
- Only organisational accounts must be used to scheduled digital and/or telephone appointments (personal accounts must not be used)
- Digital and/or telephone appointments with parents/families MUST NOT be audio recorded
- This process will only be implemented in situations where members of the clinical care team or participating site research team cannot be present on-site, to allow the continuing of study recruitment during the COVID-19 pandemic, should participating sites be impacted by lockdown restrictions

Prior to the above process being implemented by a participating site, the site must obtain approval from their local Human Research Ethics Committee (HREC)/Institutional Review Board (IRB), and further implement and follow any internal organisational policy, procedure and/or recommendation around the use of digital platforms/technologies, as required.

Figure 4. Flowchart of SAE Data Collection by Consent Pathways



7 INTERVENTIONS

7.1 Respiratory Support (PEEP) Strategies

For the purposes of this study, DR stabilisation is defined as supporting the transition to air breathing by facilitating spontaneous breathing through the creation and defence of a FRC in newly born very premature infants. We expect most infants to have achieved these goals by 20 minutes. Separation of treatment arms in this study is critical in this time period.

The POLAR Trial intervention period is defined as the first 20 minutes after the mask is placed on the infant's face at/after birth. The allocated PEEP strategy (intervention) can be ceased before 20 minutes, if clinical stability during the birth transition is achieved, and

1. The infant is ready to be moved to another location, or
2. Care is focusing on post-stabilisation interventions (e.g., umbilical line placement in the delivery room), whichever is achieved first.

CPAP can be ceased if an infant meets Site criterion.

Some infants may require ongoing resuscitation beyond 20 minutes, or it is standard practice to continue early respiratory management or golden hour bundles in the DR prior to transport to NICU. Section 7.6 details the recommended management of infants in the delivery room beyond the initial 20-minute interventional period.

Figures 5 and 6 describe the Delivery Room interventional algorithms for the study. Due to regional differences in neonatal resuscitation program training and local language, each participating site can request to amend the Static PEEP (Figure 5) and Dynamic PEEP (Figure 6) Algorithms to suit local practices, as long as these changes are only to serve training purposes and the fundamentals of the trial intervention procedures are not altered. Any alterations to the PEEP Algorithms must be approved by

the Trial Steering Committee (TSC) during site-start-up procedures and will be included in clinical education training sessions and site initiation meetings held with each participating site.

Randomisation procedures (see Section 8.0) and trial interventions will need to be applied during a busy period of clinical care with rapidly changing conditions. To overcome the risk of protocol non-compliance, random allocation (by way of opening a Randomisation Envelope; refer to Section 8.1) will occur before birth, allowing enough time for the clinical team to set the correct PEEP, and incorporate the PEEP protocol into the immediate pre-resuscitation team briefing. To further ensure protocol compliance, a laminated version of the allocated PEEP Algorithm (Dynamic or Static) will be displayed adjacent to the manometer within the DR.

Consistent with NRP guidelines on the stabilisation/resuscitation of newly born infants at birth, any respiratory support will initially be commenced using CPAP via a non-invasive interface (facemask, nasopharyngeal tube, or nasal prong. CPAP requires the infant to be spontaneously breathing. If an infant is not spontaneously breathing (apnoea) or breathing effort is inadequate (see Table 7.1 for criteria for respiratory deterioration) during CPAP delivered PEEP, then PPV should be commenced. PEEP levels can be increased during CPAP or non-invasive and intubated PPV as per the allocated PEEP protocol. At any PEEP level, if PPV is commenced this should continue unless the clinician assessed the infant to have sufficient respiratory effort to be maintained on PEEP alone (CPAP).

In both trial groups the intervention (PEEP level) will be applied using a T-piece resuscitator device that delivers manually set pressure levels via a constant bias flow of gas. The bias flow rate must be set to ensure the PEEP levels can be maintained during the 'Team Huddle' (see section 7.2). The clinician will manually set the PEEP level using a small dial at the airway opening (so it can be adjusted whilst holding a mask and T-piece over the baby's face). A manometer display provides visual feedback to ensure correct PEEP setting.

Timing of cord clamping will be performed as per each site's normal practice. The resuscitation team will assess respiratory effort, peripheral oxygen saturation (SpO_2) and/or heart rate response using pulse oximetry (right hand; pre-ductal) and/or ECG electrodes, as per site policy. SpO_2 and heart rate using pulse oximetry or ECG is widely used to guide respiratory support needs,[42] as more sophisticated methods of guiding respiratory care in the DR are lacking.[2] Current NRP guidelines recommend continuous pulse oximetry, with heart rate assessment every 60 seconds. We will use the following criteria to monitor infant responses, define ***respiratory deterioration,*** and guide response to interventions (see Table 7.1):

Table 7.1: Definition of Respiratory Deterioration and Interventions in the Delivery Room

Any of these criteria indicate ***respiratory deterioration****, and that additional resuscitative measures need to be implemented:*

- Heart Rate <100 beats per minute (bpm) **and/or**
- Apnoea **and/or**
- Increasing oxygen requirement to maintain heart rate and/or SpO_2 targets

Additional resuscitative measures will be implemented stepwise in the following suggested order:

1) Mask/interface PPV (See #3 below) may be commenced immediately at the discretion of the clinician in circumstances of significant apnoea and bradycardia. Immediate PPV should be performed in conjunction with reassessment of adequacy of airway patency and mask/interface (see Point #2) to ensure effective ventilation.

2) Active Reassessment of the adequacy of current respiratory support[i]
   a. Adjust/alter mask/interface
   b. Repositioning head to open airway
   c. Open mouth and lift jaw

3) Commencing positive pressure ventilation (PPV) at an inflating pressure of 20-25 cmH_2O depending on centre/regional guidelines (minimum 20 cmH_2O and maximum 25 cmH_2O). Prolonged PPV with inflating pressures >25 cmH_2O are not recommended in most resuscitation guidelines. Transiently increasing inflating pressures up to 35 cmH_2O is permitted if there is no chest wall rise at 25 cmH_2O inflating pressure, and the infant remains bradycardic. PPV will be delivered at a rate of 40-60 inflations/min.

4) Consider intubation with an endotracheal tube[ii]
   i. These resuscitative measures represent a modification of the NRP 'MR SOPA' algorithm [31]. The purpose is to ensure effective ventilation and delivery of any positive pressure support being provided (CPAP and PPV).
   ii. Intubation should only be performed if there is ongoing respiratory deterioration, despite PPV at an inflating pressure of 25 cmH_2O in the inspired oxygen range for intubation at the participating site, and appropriate ventilation corrective steps at the **highest allocated permissible PEEP** (6 cmH_2O Static Group; 12 cmH_2O Dynamic Group). The use of a laryngeal mask in the delivery room will be considered equivalent to intubation (whether intubation in the delivery room follows or not).

7.2 Team Huddle

It is strongly suggested that the DR resuscitation clinical team perform a brief huddle prior to the delivery of the infant. During the team huddle, the clinical team should allocate responsibilities and tasks to each participating team member involved in the DR and study procedures. Specifically:

1. Identifying and ensuring all required roles are taken by a specific individual
2. Determination/reaffirmation of trial eligibility
3. Ensure randomisation envelope for correct gestational age stratum is available
4. Perform checklist to ensure all equipment is present and functional

5. Randomisation if appropriate (see Section 8.0), including announcement to all members of the clinical team present and affirmation of the randomisation group by all clinical team members
6. Review initial steps and timing for assessment(s) for the allocated Static PEEP (control group) or Dynamic PEEP (intervention group) Algorithm (see Section 7.3-7.4), including placing a laminated version of the allocated algorithm next to the T-piece PEEP resuscitator
7. Address all questions and concerns by clinical team members
8. If time permits, briefly review the allocated intervention training video.

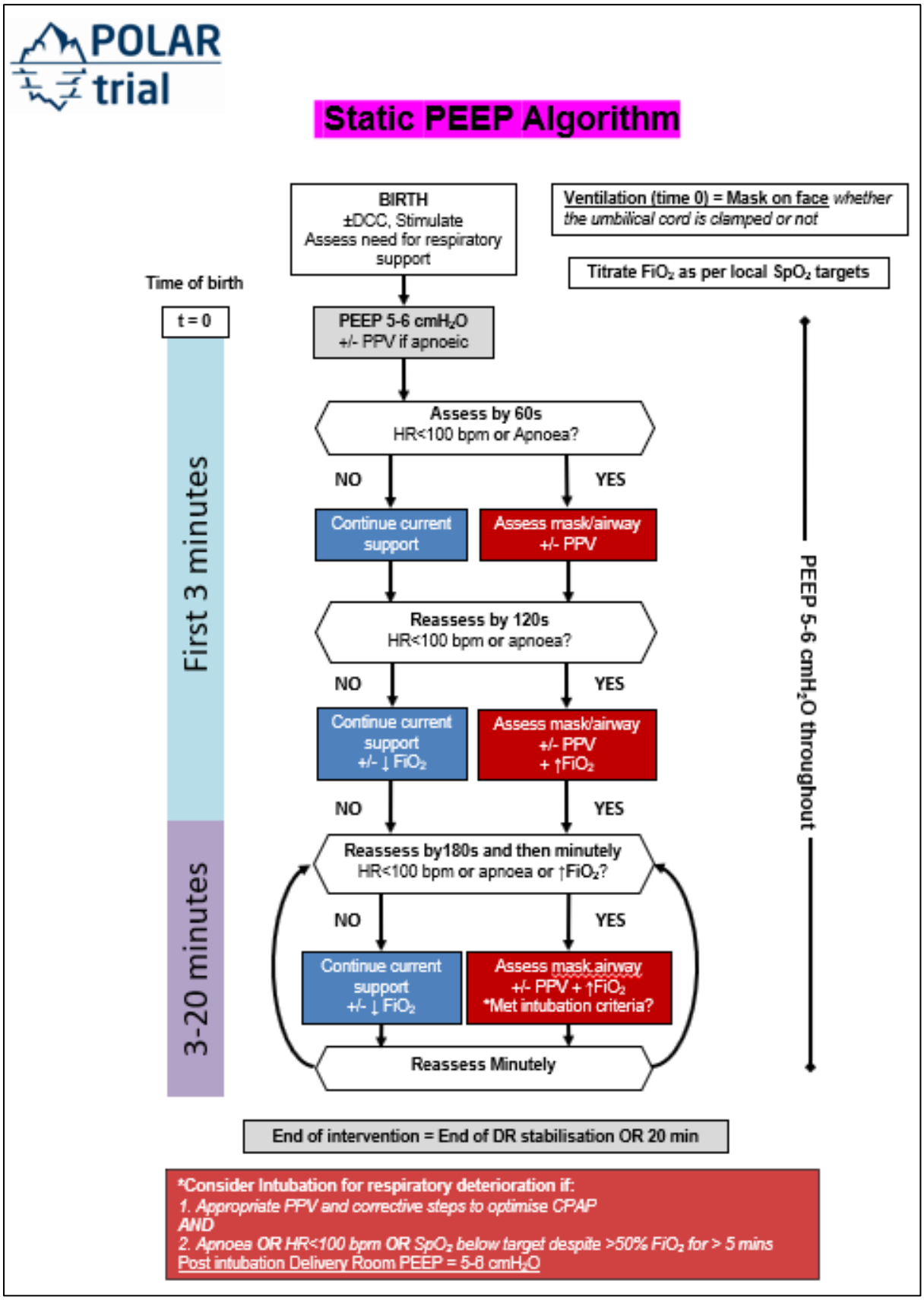
7.3 Static PEEP (Static Group; Figure 5)

Respiratory support will be as per the current NRP guidelines, including delivery of PEEP set at 5-6 cmH_2O via a T-piece resuscitator using an initial fraction of inspired oxygen (FiO_2) of 0.30 via local standard interface (facemask, nasopharyngeal tube, or nasal prong). PEEP will not be altered during the DR intervention period beyond the set 5-6 cmH_2O range.

- Cardiorespiratory status will be assessed at least every 60 seconds (more frequently if clinically appropriate or it is standard local practice to do so) from the time the mask/local interface ('mask') is placed on face.
- In the first three (3) minutes, heart rate and breathing pattern will be used to define cardiorespiratory status (Table 7.1).
- After three minutes, heart rate, breathing pattern and SpO_2 levels will be used to assess cardiorespiratory stability.
- Prior to three minutes, SpO_2 should only be used if the clinical team has reliable pulse oximetry measurements available.
- If an infant meets the heart rate, respiratory effort and/or oxygenation criteria for ***respiratory deterioration*** (Table 7.1) and the measures detailed in Table 7.1 are being followed, then increases in FiO_2 are permissible in increments depending on local practice and/or discretion of the Site Investigator, such as from 0.3 to 0.5 to 0.7 to 1.0, and then same decrements to air if SpO_2 is above target range.
- FiO_2 should not be increased unless active reassessment of the adequacy of current respiratory support level has been made, and reversible causes addressed.
- If PPV is commenced, it should continue until the clinician assesses the infant to have sufficient respiratory effort to be maintained on PEEP alone.

The PEEP algorithm is to be followed for the first 20 minutes after the mask is placed on the infant's face, or until clinical stability during the birth transition is achieved and the infant is ready to be moved to another location, or care is focusing on post-stabilisation interventions, whatever is achieved first. CPAP can be ceased if an infant meets Site criterion.

Figure 5: Static PEEP Algorithm Template



7.4 Dynamic PEEP (Dynamic Group; Figure 6)

Resuscitative care will be as per the static PEEP group except for two fundamental differences:

1. If the criteria for respiratory deterioration are met, PEEP will be increased before escalating PPV as detailed below.
2. If an infant meets the criteria of cardiorespiratory improvement detailed below at a PEEP >8 cmH_2O, then the PEEP will be decreased.

In all infants, the initial PEEP will commence at the lowest permissible interventional PEEP level of 8 cmH_2O.

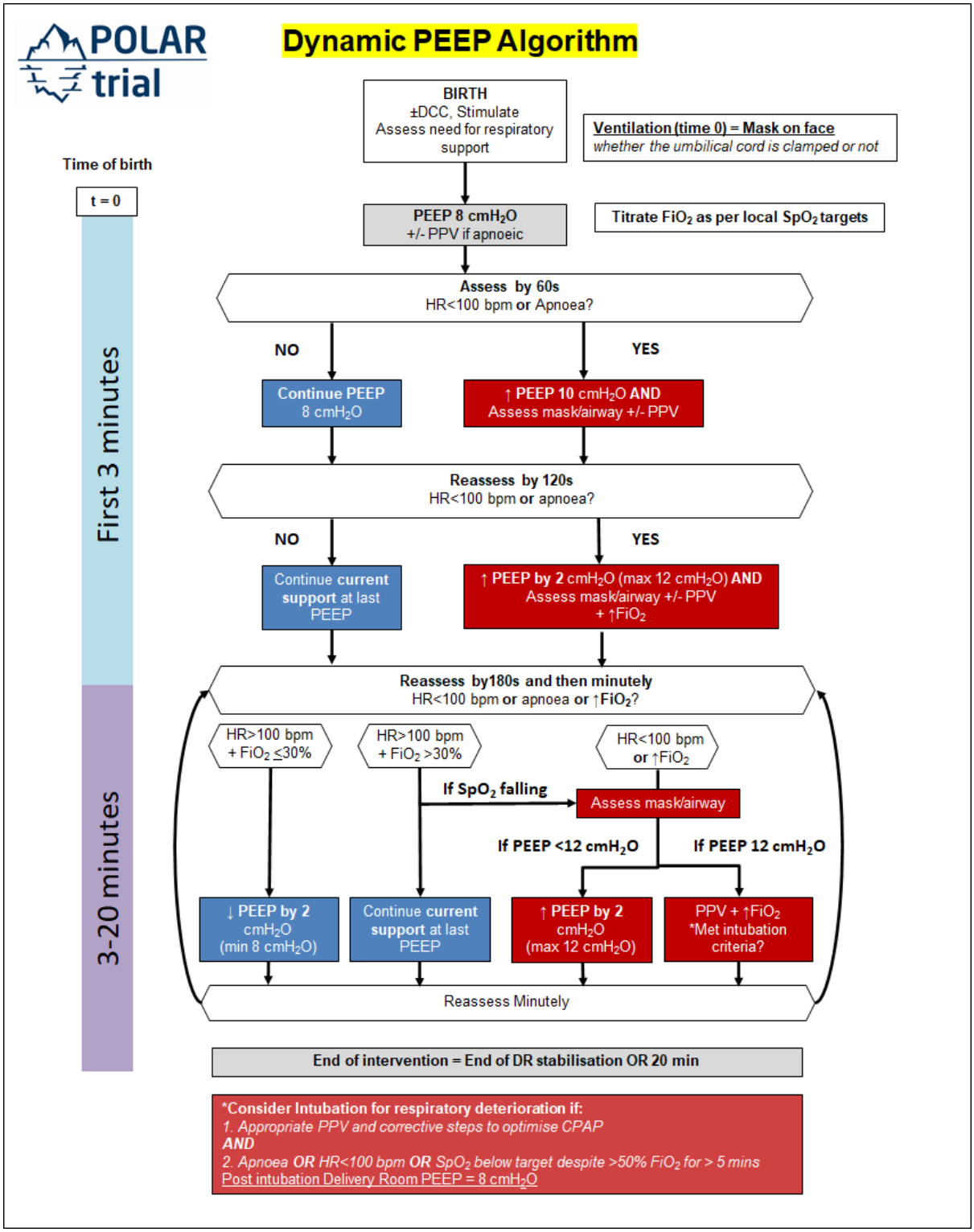
- As per the Static PEEP group, cardiorespiratory status will be assessed at least every 60 seconds (more frequently if clinically appropriate or it is standard local practice to do so).
- ***Respiratory deterioration*** at 60 seconds at 8 cmH_2O PEEP***, or at any time after, if the infant was initially stable but later deteriorates at 8 cmH_2O PEEP*** will be managed by correcting reversible causes **and** increasing PEEP to 10 cmH_2O (with or without PPV as per Control Group).
- PEEP will then be further increased to 12 cmH_2O if there is continued respiratory deterioration after 60 seconds at 10 cmH_2O, ***or at any time after, if the infant was initially stable but later deteriorates at 10 cmH_2O PEEP***.
- At 12 cmH_2O PEEP reassessments should continue at least every 60 seconds (more frequently if clinically appropriate or it is standard local practice to do so) as per Static PEEP Group.
- Further ***respiratory deterioration*** will be managed as detailed in Table 7.1, including intubation if required.
- At any PEEP level, if PPV is commenced this should continue unless the clinician assessed the infant to have sufficient respiratory effort to be maintained on PEEP alone.
- PEEP levels can be increased during PPV or CPAP.

If an infant shows evidence of respiratory improvement during resuscitative care the PEEP will be reduced to the previous PEEP level (that is reduced stepwise by 2 cmH_2O). Improvement in respiratory status is defined as if heart rate is >100 bpm and FiO_2 <0.30 for at least 60 seconds. Further stepwise reductions in PEEP (no lower than 8 cmH_2O) are indicated if respiratory improvement continues at least 60 seconds after a PEEP reduction.

Importantly, if after any PEEP reduction an infant meets the criteria for ***respiratory deterioration*** again, then the PEEP must be increased back to the last stable PEEP level in conjunction with additional resuscitative measures and FiO_2 increase, and the algorithm followed accordingly (see Section 7.5 for details on PEEP levels if the criteria for intubation are met and the infant is intubated).

The PEEP algorithm is to be followed for the first 20 minutes after the mask is placed on the infant's face, or until clinical stability during the birth transition is achieved and the infant is ready to be moved to another location, or care is focusing on post-stabilisation interventions, whichever is achieved first. CPAP can be ceased if an infant meets Site criterion.

Figure 6: Dynamic PEEP Algorithm Template



7.5 Criteria to Intubate (Insert Endotracheal Tube) during the Delivery Room Intervention Period (Failure of Non-Invasive Support)

Irrespective of the allocated PEEP strategy, the following criteria will be used to define failure of non-invasive support and initiate intubation and placement of an endotracheal tube for PPV during the intervention period in the Delivery Room, once the highest permissible PEEP has been delivered (Table 7.2):

Table 7.2: Criteria to Intubate and Insert ETT during the Delivery Room Intervention Period (Failure of Non-Invasive Support)

- Apnoeic and bradycardic despite appropriate positive pressure ventilation via mask or another interface (see 7.1)

  OR
- Receiving appropriate corrective resuscitative steps to optimise CPAP +/- positive pressure ventilation at the highest allocated PEEP

  AND
  - Meets respiratory deterioration criteria (See Table 7.1)

    AND/OR
  - Has a required FiO_2 ≥0.5 to maintain target SpO_2 ranges for **at least** 5 minutes at any time after the first 3 minutes of allocated respiratory support despite appropriate corrective steps.

Notes:

1. Intubation should not be performed unless all corrective resuscitative measures have been performed **and** response assessed, **and** PEEP increased if in the Dynamic PEEP group.
2. Each site should observe their local practice/guidelines for FiO_2 thresholds when intubation is indicated., however, FiO_2 must be at least ≥0.5. Sites must discuss local FiO_2 thresholds with the POLAR Trial Executive Committee (TEC) during site start-up procedures so that documentation of site practice can be recorded.
3. **If intubated, PEEP during endotracheal tube positive pressure ventilation will be delivered at 5-6 cmH_2O (Static PEEP group) or 8 cmH_2O (Dynamic PEEP group) during the intervention period.**

If apnoea is due to foetal exposure to general anaesthesia (and no other criteria for intubation are met), intubation can be deferred for 10 min as long as effective PPV via a non-invasive interface can be delivered. All other aspects of the allocated intervention should be followed.

7.6 Delivery Room Management for Infants remaining in the Delivery Room Post-Intervention Period

If stabilisation in the delivery room continues beyond 20 minutes, PEEP levels can be applied as per standard practice at site. Although, it is **recommended** that the final PEEP level in use during the intervention period be continued, and that infants **remain in their allocated treatment groups until departure from the DR if the infant is clinically responding**.

For ongoing DR stabilisation beyond 20 minutes, and during transfer, the following are permissible:

1. **Static Group:** For non-intubated infants, an increase of PEEP up to 8-10 cmH_2O to prevent intubation, **if standard practice at site**.

2. **Dynamic Group:** For intubated and non-intubated infants, stepwise weaning PEEP below 8 cmH_2O (minimum 5-6 cmH_2O) for stable infants with FiO_2 <0.30 **if standard practice at site**.

After 20 minutes, the Dynamic PEEP algorithm is NOT permitted in either group.
During transfer from the delivery room, PEEP can be applied as per site practice, but it is recommended that infants remain in their allocated treatment groups.

7.7 Recommendations for Post-Resuscitative (NICU) Management

Participating sites should use site specific therapies for respiratory management in the NICU. Use of caffeine treatment will be as per local site practice for all infants admitted to NICU on CPAP, or before extubation. Mode of invasive ventilation, CPAP delivery device and nasal High-Flow therapy during non-invasive support weaning will be at the discretion of each centre. The use of non-invasive intermittent positive pressure ventilation to prevent intubation due to **apnoea** in the first 72 hours of life will be allowed if standard practice in a study site.

Criteria for respiratory care in the NICU that may influence outcomes and safety will be provided and compliance documented, specifically the use of PEEP during CPAP and decisions to intubate in the first 72 hours (when the reason for intubation is likely to be due to primary RDS and thus most likely to represent CPAP PEEP-treatment failure; Table 7.3) and extubate [26, 33, 36]. The mode of invasive respiratory support (via an endotracheal tube) will be at the discretion of each centre, including the use of high-frequency ventilation. During conventional ventilation, each centre will be encouraged to synchronise all inflations and use volume targeted ventilation.

PEEP levels during CPAP after admission to the NICU with the first 72 hours will not be mandated. Sites will be encouraged to maintain the allocated PEEP level on admission, and **consider**:

1. Use of PEEP within a range of 5-8 cmH_2O
2. Increase of PEEP up to 8 cmH_2O to prevent intubation
3. Using a stepwise strategy of weaning PEEP from 8 cmH_2O to a minimum 5-6 cmH_2O during disease recovery (stable work of breathing, no apnoea and/or FiO_2 ≤0.30).

If conventional ventilation is commenced, PEEP levels will not be mandated but sites will be encouraged to use a PEEP between 5-8 cmH_2O as per each sites' practice. An 'open lung' recruitment approach will be permitted to correct atelectasis and identify an optimal mean airway pressure setting if high-frequency oscillatory ventilation is used in centres who have expertise in the approach, and it is existing site practice.

Bundles of non-invasive respiratory care within each site, for example minimally invasive methods of administering surfactant (including in the Delivery Room), will be permitted and will not constitute treatment failure unless an endotracheal tube used to administer surfactant (e.g., INSURE) is in situ for more than 4 hours.

As receiving invasive mechanical ventilation is an independent predictor of long-term respiratory outcomes and other morbidities the POLAR trial will have recommended criteria for intubation in the first 72 hours (Table 7.4) and extubation in the first 10 days of life in the NICU.

Table 7.3: Guidelines for intubation in the NICU within the first 72 hours after birth (Failure of Non-Invasive Support)

Failure of Non-Invasive Support in the NICU:

Treatment failure is reached once an infant is receiving **maximal non-invasive therapy** used at the specific centre, **plus** at least one of:

1. **Apnoea** unresponsive to stimulation or caffeine citrate treatment (>6 episodes requiring stimulation in 6 hours or requiring >1 episode of PPV in a 24-hour period)
2. **Sustained increase in oxygen requirement to maintain SpO_2 within local targets** (discretionary at FiO_2 ≥0.30[1] and mandatory at FiO_2 ≥0.50)[1]
3. **Respiratory acidosis** not responsive to treatment; defined as an arterial or capillary pH ≤7.20 *with* partial pressure of carbon dioxide (PCO_2) ≥65 mmHg
4. Emergency intubation at clinician discretion.

7.8 Extubation Guidelines in the NICU Within the First 10 Days after birth

Extubation is recommended within 24 hours of meeting all of the following:

1. Mean airway pressure ≤8 cmH_2O
2. PCO_2 ≤55 mmHg (arterial or capillary)
3. pH ≥7.25
4. FiO_2 ≤0.40 with SpO_2 within local targets; and
5. Adequate respiratory effort.

Extubation can be attempted from higher ventilator settings or higher PCO_2 thresholds if deemed appropriate. The use of extubation predictive tests[43] will be at the sites' discretion. Non-invasive support post extubation can be delivered at a PEEP level of 5-8 cmH_2O at the site's discretion irrespective of initial allocated study group. The use of post-extubation dynamic PEEP ('open lung') manoeuvres during CPAP within the first 10 days of life are not recommended.

7.8.1 Intervention Modifications

Beyond those detailed in Sections 7.1-7.3, no additional modifications to the respiratory support protocols within the delivery room for each group will be permissible during non-invasive support.

7.8.2 Excluded Interventions

The following interventions **are not permitted during the trial**:

1. The use of any form of Sustained Inflation (SI). For the purpose of the POLAR trial, a SI is defined as an intentional positive inflation pressure provided for **longer than 5 seconds** via any ventilation or resuscitative positive pressure device.
2. A delivery room resuscitative respiratory device that does not have a direct titratable PEEP delivery system via a T-piece, such as a flow-inflating device (even with a PEEP adaptor) or the Benveniste Valve™ (Dameca, Löwenstein Group, Rødovre, Denmark).

7.8.3 Permitted Interventions

The following interventions **are permitted during the trial** using existing local site practice:

1. Type, timing, and method of exogenous surfactant administration
2. Physiological or delayed cord clamping/milking
3. Suction of the mouth/nose to facilitate delivery of positive pressure and/or airway interventions
4. Type and timing of post-natal steroid administration for respiratory indications.
5. After 36 weeks PMA, site specific therapies for respiratory management as part of a chronic BPD bundles of care are permitted, as per local site practice (this includes the use of PEEP levels ≥10 cmH_2O if standard practice at Site).

Details of the above interventions will be recorded on the relevant sections of the CRF.

7.8.4 Concurrent Research Enrolment

The POLAR Trial Steering Committee (TSC) encourages and supports concurrent enrollment with other clinical trials unless trial compromises the integrity of the other trial outcomes. This includes trials with death and/or BPD as primary outcomes as long as the timing of interventions are sufficiently separated. Concurrent trial enrolment will enhance recruitment efforts at POLAR Trial participating sites.

The policy on Concurrent Trial Enrolment is as follows:

1. All randomised trials that likely involve participants who are also eligible for the POLAR trial, must be discussed with the POLAR Executive Committee, and the protocols shared with the Sponsor-Investigator, prior to co-enrolling any infants.
2. All such studies may or may not be compatible with the POLAR trial, and a full discussion will be undertaken with all parties to resolve potential for co-enrollment.
3. Enrollment of POLAR participants in concurrent studies that involve consent for the child and family must be documented within the participant's medical record and on the Final NICU CRF within the POLAR REDCap Data Management System (DMS).

8 RANDOMISATION AND BLINDING

A statistician not directly involved in the analysis of the study results will prepare the randomisation schedule using permuted block randomisation of variable length, an allocation ratio of 1:1 and stratification by study centre and by PMA (23-25+6 weeks GA and 26-28+6 weeks GA) to maintain balance between the two PEEP groups. Infants born as one of multiples (twins and above) will be randomised independently.

8.1 Randomisation Process in the Delivery Room (DR)

An infant is randomised into the POLAR Trial when he/she has been determined as eligible and a randomisation envelope has been opened. The following steps should be followed:

- The randomisation process will occur in the Delivery Room (DR) ideally before the infant is born and with sufficient time to allow a Team Huddle
- Randomisation must occur prior to the delivery of any PEEP
- The resuscitation team leader/neonatologist confirms the infant's estimated GA

- The resuscitation team leader/neonatologist will instruct the responsible member of the resuscitation team to select the next envelope in the sequence based on the infant's estimated GA stratum (23-25 weeks GA or 26-28 weeks GA)
- The randomisation envelope is opened
- The team member should loudly and clearly announce the randomisation group allocated
- All team members acknowledge the randomisation group (closed loop communication), identify, and confirm correct laminated trial algorithm to be used
- Address all questions and concerns.

Sealed opaque allocation envelopes will be provided by the Data Coordinating Centre (DCCe). Each envelope will have the site ID and the randomisation number on a sticker on the outside and will be colour coded by stratum. The envelopes must be kept in close proximity to the Delivery Rooms at participating centres, at an appropriate location to be determined and documented during site start-up procedures. The envelopes in each stratum will be sequentially assigned to infants in that stratum.

Once an infant is randomised, the clinical care team/research team must enter the participant into the POLAR REDCap Data Management System (DMS), within 24-48 hours of birth, irrespective of whether deferred consent has been employed. The randomisation number assigned and date of randomisation, along with minimal data around mode of consent and confirmation of eligibility, will need to be entered at this time. Remaining data entry may occur at a later time.

Please refer to the POLAR Manual of Procedures (MoP) document for further details regarding the Randomisation and Participant Enrolment Process.

8.2 Concealment Mechanism

Web-based randomisation may inhibit recruitment as logging onto a computer system or using a smartphone is not always feasible in the DR. Envelopes allow the clinical team to immediately access randomisation allocation, can be taken to any site of imminent birth, and have been successfully used in previous DR studies[26, 35, 36].

Before the infant's imminent delivery in the DR/resuscitation unit, the person responsible for opening the randomisation envelope should select the next envelope in the sequence based on the infant's estimated GA. The envelope should be nearby and ready to open for allocation once the lead clinician has verified eligibility.

If a randomisation envelope is opened but not used, that randomisation label should not be used for another qualified infant, and it should be reported to the Trial Coordinating Centre as soon as possible, as this will alter the randomisation scheme.

If a randomisation envelope is opened in error, the protocol deviation section of the Eligibility and Randomisation CRF should be completed, along with an Event of Non-Compliance Report form and forwarded to the Trial Coordinating Centre (TCC), explaining the situation including details of any corrective and preventative actions (CAPA) taken by the site, to ensure errors are minimised in future.

Such envelopes should also be saved and returned to the Trial Coordinating Centre (TCC) for verification. The deviation should also be entered into the POLAR Data Management System (DMS).

Masking/blinding of the intervention is not practical. Allocation will be unknown at the time of eligibility determination.

Further details on the Randomisation process are outlined in the POLAR Manual of Procedures (MoP) document.

8.3 Breaking of the Study Blind

8.3.1 On Study

Not applicable as the intervention allocation will be known to the clinical team within the DR following randomisation, as well as the clinical care and research teams at site.

Should it be required for the Sponsor-Investigator, members of the Trial Coordinating Centre (TCC) or Data Coordinating Centre (DCCe) to be unblinded in certain situations, procedures for unblinding as outlined in the POLAR Unblinding SOP, will be followed.

8.3.2 On Completion of the Study

After database lock, the trial statistician will request the randomisation list from the independent statistician who generated it and break the blind for the full sample of participants.

9 STUDY VISITS AND PROCEDURES

9.1 Study Timeline and Schedule of Assessments

Table 9.1 details the study timeline and schedule of assessments.

In all infants, screening will be conducted in the antenatal period or immediately prior to delivery. Randomisation, allocation of intervention and delivery of assigned intervention will occur in the Delivery Room (DR), as detailed in Sections 7.0 and 8.0.

Data related to protocol adherence, pre-specified primary (refer to Section 10.1) and secondary outcomes (refer to Section 10.2) will be collected to capture the DR care and then NICU management in the first 24 hours of life (after discharge from DR), the first 10 days of life, at 36 weeks PMA, and as appropriate throughout the entire hospital stay.

A follow-up visit will occur at 24-months PMA to assess for neurological and respiratory outcomes consistent with clinical long-term outcome programs. In addition, relevant maternal/perinatal data, and adverse events (AEs), serious adverse events (SAEs) and other safety events/risks will be specifically documented (as detailed in Section 11.0).

Table 9.1: Study Timeline and Schedule of Assessments

TIMEPOINT	SCHEDULE	ASSESSMENTS	
$t_{pre\text{-}delivery}$	Screening/Eligibility *(Between 23+0 (or earlier if appropriate) and 28+6 weeks GA)*	A	
		Prospective Consent *(Antenatal Consent)*	***Waiver of Prospective Consent*** *(Deferred Consent)*
$t_{pre\text{-}delivery}$	ENROLMENT *(At the time of randomisation)*	B	Nil
t_0	RANDOMISATION AND ALLOCATION TO INTERVENTION		
t_0	Delivery Room *(At the time of birth)*	C	C
t_1	NICU - Day 1 *(Assessment completed 24 hours post birth)*	D	D
t_{NICU}	Following Admission to NICU	Nil	B
t_{10}	NICU - Day 10 *(Assessment completed Day 10 post birth)*		D
t_{prn}	NICU - Anytime	E	E
T_{prn}	AE/SAE Assessment *(As they occur - AE Reporting up to Day 28 of life. SAE Reporting up to 36-Weeks PMA)*	F	F
$t_{36\ PMA}$	36-weeks PMA *(Primary Endpoint Assessment. Assessment to be completed on the date determined to be 36+0 to 36+6 weeks corrected gestational age.)*	G	G
$t_{44\ PMA}$	44-weeks PMA, or death, or at the time of discharge home *(Secondary Endpoint Assessments. Assessments to be completed at Discharge Home, Death or 44 weeks PMA, whichever occurs first (+/- 5 days))*	H	H
$t_{24\ months}$	24-months PMA *(Long-term Secondary Endpoint Assessment. Assessment to occur at 2-years of age corrected (+/- 2 months))*	I	I
A	Screening of eligibility criteria (mothers presenting with threatened preterm delivery <29 weeks PMA).		
B	Approach parents whose infant meets eligibility criteria (or parents of infants meeting eligibility criteria and randomised in centres permitting waiver of prospective consent (i.e. deferred consent). Refer to Figure 3 for consent process.		
C	Collection of protocol intervention applied, physiological measures of cardiorespiratory well-being and clinical events will be recorded minutely during management in the DR using an algorithm-specific case report form (see Section 10.2), PLUS the collection of relevant antepartum data that may influence delivery room care.		

D	Data related to secondary outcome measures and response to intervention as detailed in Section 9.2 during the first 24 hours of life (from admission to NICU), and then the first 10 days of life.
E	Data related to secondary outcome measures and response to intervention as detailed in Section 9.2 following the first 10 days of life (from admission to NICU).
F	Assessment and reporting of ***Adverse Events (AEs) and/or Serious Adverse Events (SAEs)*** should they occur at any time during hospital stay or before 36 weeks PMA.
G	Assessment of Primary Outcome measures (death or BPD) (as per Section 10.1) and Hospital Stay secondary outcomes (as per Section 10.2).
H	Assessment of neurological and respiratory outcomes consistent with clinical secondary outcome programs.
I	Assessment of long-term outcomes consistent with two-year follow-up programs.

9.2 Screening

Screening data will ascertain whether an infant is eligible for the study (or not), the process of consent and outcome of that process and randomisation if it occurred. Screening will occur prior to an infant's birth as detailed in Section 6.4. The clinical care team/research team at each site will maintain a screening log of all screened mothers-infants, indicating who is eligible and who is not, and of eligible mothers who have consented to the study and who have refused study participation. Screening information (i.e., the Screening Log) will be recorded and maintained directly within a POLAR Data Management System (DMS) i.e., REDCap. Note: this Screening Database is maintained separate to the main POLAR trial database. Refer to the POLAR CRF Completion Guidelines for further information regarding data entry.

9.3 Delivery Room Data

1. **Eligibility and Randomisation Data:** The following data will initially be recorded within the participant's medical record, prior to data entry into POLAR Data Management System (DMS) i.e., REDCap:
    - Confirmation that the infant meets the eligibility criteria for the study (i.e., all of the inclusion and none of the exclusion criteria)
    - Documentation of randomisation number and date of randomisation; and
    - Documentation of mode of consent, i.e., antenatal or deferred
    - Allocation of Participant Identification Number (PID#).

2. **Real-Time Delivery Room Data:** A paper case report form (CRF) will be available to allow for real-time data collection pertaining to the clinical interventions provided within the Delivery Room (DR), physiological markers of cardiorespiratory status and delivery. The Delivery Room (DR) Management paper CRF is an identical copy of the electronic CRF appearing within the POLAR Data Management System (DMS), to allow for ease of transcribing of the collected data from paper into the database. The data variables to be collected include:
    - The assigned intervention and length (in minutes) of the delivered intervention
    - Time of delivery/birth
    - Use of Delayed Cord Clamping (DCC) and timing
    - Delivered PEEP settings/level
    - Positive Inflating Pressure (PIP) levels (if used)
    - Fraction of inspired oxygen (FiO_2) delivered

- Time the mask or respiratory support method was applied to face (time zero)
- Intubation status
- Heart Rate (HR); lowest and highest HR reading
- Oxygen Saturation (SpO_2) levels
- Highest modified oxygenation index (SpO_2/ FiO_2) (calculated post hoc)
- Documentation of other DR interventions and/or medications used
- Documentation of the role & designation of staff present in the DR
- Final respiratory settings on departure from delivery room
- Final clinical outcome in the delivery room.

3. Antepartum Data: These data will be completed, and entered directly into the POLAR DMS at a suitable time, either before or after delivery, to allow for the different permutations of consent, including:
    - Maternal medical history
    - Medication history
    - Demographic information of the mother and infant, including:
        - Mother's year of birth
        - Mother's initials (not mandatory to provide)
        - Mother's race/ethnicity (if consented to provide)
        - Infant's full date of birth, time of birth and gender
        - Infant's initials (not mandatory to provide)
    - Pregnancy data, including:
        - Gestational age (in weeks/days)
        - Birth weight (g)
        - Gravida/Plurality of the pregnancy
        - Mode of delivery and reason
        - Reason for preterm birth
        - Documentation of the use of any antenatal steroids, or other emergency antenatal/perinatal medication
        - Documentation of any adverse events and/or safety issues.

The real-time delivery room data must be collected at and during delivery (and implementation of intervention). As such, these data will be collected before retrospective consent has been obtained (if antenatal consent cannot be obtained). These data are fundamental to understanding protocol/intervention compliance and interpreting the trial outcomes, and hence, cannot be collected in retrospect. In the situation where a parent/guardian does not grant permission to use these data, the data will be destroyed/deleted and removed from the study. The only exception will be in the situation of an SAE as detailed in Section 6.5.2. In this situation, the real-time delivery room data will constitute a part of the aggregate data (de-identified) for safety analysis.

The real-time Delivery Room data allows identification of the allocated study intervention. These data will be entered into the "Delivery Room Protocol Intervention" CRF, which is a hidden CRF within the POLAR DMS that is not visible to the trial statistician and members of the TCC.

Appreciating the complex and dynamic process of preterm delivery room care, some baseline data variables can be collected after an infant is admitted to the NICU. Refer to the POLAR Manual of Procedures (MoP) for further details.

9.4 NICU Stay, End of NICU Course and Discharge/Study Withdrawal/44-Weeks PMA Assessment/Data

The clinical care team/research team will record data relating to the clinical course during the first 24 hours, 72 hours and 7 and 10 days after birth, and then relevant secondary outcomes during NICU stay until hospital discharge, death, study withdrawal or 44-weeks PMA (whatever comes first) for each infant; including:

- Use of inotropes
- Use of supplemental oxygen, including level of FiO_2 at 24 hours after birth, 72 hours, and midday on 7 and 10 days after birth
- Highest PEEP used during the first 72 hours after birth, and at 24 hours, 72 hours and at midday on 7 and 10 days after birth
- Documentation regarding invasive mechanical ventilation at 7 and 10 days
- Survival status / date of death (during hospital stay, if applicable) / reason for death
- Documentation of any adverse events and/or safety issues
- Relevant secondary outcomes as detailed in Section 10.2, including:
  - Use of postnatal steroids
  - Incidences of retinopathy of prematurity (ROP), significant brain injury (IVH, periventricular leukomalacia), pneumothorax and pulmonary interstitial emphysema (PIE)
  - Duration of invasive respiratory support
  - Duration of non-invasive support
  - Requirement for oxygen at discharge

In addition, relevant baseline maternal, antenatal, and demographic data not collected whilst in the Delivery Room will also be collected. These will be recorded from medical notes, investigations, and bedside monitors.

9.5 36-Weeks PMA Assessment/Data

The primary outcome is death or Bronchopulmonary Dysplasia (BPD) at 36 weeks PMA, as assessed using the Modified Walsh definition and standard oxygen reduction test [44,45]. The final on-study visit will be completed at the latter of each of these outcomes (death or BPD). Data will be collected on the primary outcome.

The 36-week BPD Assessment should occur on the date determined to be 36+0 to 36+6 weeks corrected gestational age (CGA).

If the BPD assessment is completed outside of the 36+0 to 36+6 weeks CGA assessment window, as the participant was discharged home from hospital early self-ventilating in air (SVIA) before 36+0 weeks CGA, then these participants will be coded as not having BPD. Should the condition of the participant change within the 36-weeks CGA (e.g. they are re-admitted to any hospital between discharge home and 36+6 weeks CGA), then the participating site must update the 36-Week CGA BPD Assessment CRF, if applicable.

However, this is a very unlikely and debatable* scenario as the most common causes for hospital re-admission will be:

1) A new respiratory tract viral infection; and/or
2) Aspiration or feed related problems that cause a baby to be readmitted and placed on O_2.

**Generally these hospital admissions do not relate or are not features of BPD but rather unique entities, however, technically the current BPD Assessment criteria does not account for mitigating circumstances.*

9.6 24-Month PMA (Follow-Up Visit) Assessment/Data

A follow-up visit will occur at 24-months PMA (+/- 2 months) to assess for respiratory and neurological outcomes, if 2-year follow-up visits are Standard of Care (SoC) practice for the participating site.

Collection of follow-up data should occur within what is standard of care practice for the participating site. If these data cannot be obtained from the medical records (i.e., via a formal neurodevelopmental

assessment) or if the participant does not attend for an in-person follow-up visit, a telephone consultation (e.g., via telehealth) with parent(s) may be completed, **if this is standard of care practice (SoC)** for the participating site, when in-person visits are not able to be performed.

Alternatively, if neither a formal neurodevelopmental assessment nor telephone consultation is completed, participating sites have the option of forwarding a Direct-to-Parent Survey to parents for completion.

The below table provides an order of recommended Follow-Up Assessment pathways and corresponding data collection methods that should be considered at participating sites:

Table 9.2: Order of Recommended Follow-Up Assessments and Data Collection Methods

Follow Up Pathway		Data Collection Method
1.	Formal Neurodevelopmental Assessment conducted via a return in-person visit, as **Standard of Care (SoC) at site**	Site accesses and reviews data from Formal Neurodevelopmental Assessment via your medical record. Site completes the POLAR 2-Year FU CRF via direct data entry.
2.	Conduct Phone Consult / Telehealth / Video Consult Appointment, **as Standard of Care (SoC) at site**, and if your site does NOT undertake a Formal Neurodevelopmental Assessment	Site contacts parent via telephone or arrange telehealth appointment if this is within SoC for the site. Site delivers questions over the phone for parents to answer. Site disseminates PARCA-R survey to Parent via unique REDCap link. Site completes the POLAR 2-Year FU CRF via direct data entry. Parent completes PARCA-R via Direct-to-Parent Survey. This questionnaire includes: 1. General health assessment questions 2. PARCA-R Parent Questionnaire (completed via Direct-to-Parent Survey via unique REDCap link)
3.	Dissemination of Direct-to-Parent Survey if you are unable to undertake Follow-Up #1 and/or #2 listed above *Refer to Section 9.6.1 below for further information.*	Site contact parents via phone or email initially to confirm contact details. Site disseminates Direct-to-Parent Survey via unique REDCap link. This parent questionnaire includes: 1. General health assessment questions 2. PARCA-R Parent Questionnaire Parent completes both general health assessment questions and PARCA-R, via Direct-to-Parent Survey, via unique REDCap link.

The Two-Year Follow-Up CRF in the POLAR Trial database MUST be completed for all participants regardless of whether a formal follow-up visit was undertaken.

The following data will be recorded (if available):

- Date and cause of death (if applicable)
- Documentation of general gross motor ability and cognitive ability

- Documentation of any visual impairment or blindness
- Documentation of any hearing impairment or deafness
- Duration of oxygen therapy after discharge (if applicable)
- Documentation of any hospital admissions for a respiratory cause.

Please refer to the POLAR Follow-Up Manual for further information on data entry requirements.

9.6.1 24-Month PMA (Follow-Up Visit) – Parent Questionnaire

If neither an in-person follow-up visit or a direct telephone or telehealth consultation cannot be performed, parents will be invited to complete an online questionnaire, which includes a brief general health assessment and a validated child development assessment aimed at parents (PARCA-R Questionnaire; Dev Med Child Neurol 2004; 46:389–97)[46], if permissible within regional data protection and privacy regulations. The PARCA-R Questionnaire is a parent completed questionnaire that can be used to assess children's cognitive and language development at 24 months of age.

The parent questionnaire will be administered via a web-based survey located on a secure server in Melbourne, Australia. The participant-specific link to the parent questionnaire, and any alerts/reminders disseminated (where necessary), will be sent electronically to parents by the clinical care teams/research teams based at each participating site, thus maintaining participant confidentiality.

No identifying information/data will be revealed to members of the study team outside of the participating sites, in the dissemination or completion of the PARCA-R questionnaire. The Sponsor or members of the Trial Coordinating Centre (TCC) will not have access to any identifiable data.

Given the international nature and reach of the POLAR Trial, the general health and PARCA-R questionnaires haves been translated into other languages will be made available to participating sites in the following languages for dissemination to parents: English, Dutch, Polish, German, French, Italian and Spanish.
The PARCA-R questionnaire will seek information on the child's development and speech. No additional information will be collected beyond what had previously been planned.

Please refer to the POLAR Follow-Up Manual for further information.

9.7 Participant Withdrawal of Consent

9.7.1 Reasons for Withdrawal and Participant Discontinuation from Study Participation

Parents are free to withdraw their infant from the study at any time. Withdrawing from the study will not affect their access to standard intervention or their relationship with the hospital and affiliated health care professionals. Withdrawal of consent could be made at any time after the birth of the infant if randomised.

The Site Principal Investigator may withdraw an infant from study participation if the infant:

1. Is found to have conditions listed in the exclusion criteria after the infant is randomised and/or intervention applied. For example, this may include an alternative cause of respiratory failure, or major congenital anomaly, that was not known at the time of randomisation but identified at a later date (for example trachea-oesophageal fistula and oesophageal atresia or upper airway obstruction). This may include diagnoses requiring a genetic, imaging, and other investigative tests that cannot readily be used in the Delivery Room. These infants will be replaced.
2. Decision to withdraw consent from trial is requested by the participants parents/guardians

3. Site Principal Investigator determines it is in the best interest of the participant.

When the Research Staff becomes aware of a study withdrawal, the clinical care team/research team should contact the Trial Coordinating Centre informing the Sponsor of the withdrawal.

Every effort should be made to obtain information on participants who withdraw from the study. The primary reason for withdrawal from the study should be documented in the "Study Withdrawal" CRF, noting that participants themselves do not need to provide a specific reason for withdrawing.

No further data entry for events occurring after the date of withdrawal is required for withdrawn participants.

An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of infants by parents/guardians should be avoided. Should a participant's parents decide to withdraw their infant from the study, all efforts should be made to complete and report the observations, as thoroughly as possible, up until the date of withdrawal.

9.7.2 Handling of Withdrawals and Losses to Follow-Up

When a consented participant withdraws from the study, any existing data already collected will be retained as the research is being legally processed as a task in the public interest. When a participant withdraws from the study, the reasons for withdrawal shall be recorded by the Site Principal Investigator (or delegate) on the "Study Withdrawal" CRF.

Every effort should be made to obtain information on participants who withdraw from the study. The primary reason for withdrawal from the study should be documented in the "Study Withdrawal" CRF. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of infants by parents/guardians should be avoided. Should a participant decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, up until the date of withdrawal.

9.7.3 Replacements

Infants enrolled in the study who are withdrawn will not be replaced as the sample size calculation allows for a 5% drop out rate. However, the infant will be replaced in situations where:

- The infant is subsequently identified as having conditions listed in the in the exclusion criteria (see Section 6.2.2), or
- The infant was identified as still born post randomisation/birth.

9.8 Trial Closure

The trial may be extended in duration if recruitment has not proceeded at the expected rate. The end of the trial will be defined as the date when the trial database is locked. An end of trial declaration will be submitted to all relevant HREC's/IRB's, as required by local regulations.

Decisions and recommendation on trial closure may be made by:

- POLAR Trial Steering Committee (TSC)
- POLAR Independent Data Safety Monitoring Committee (DSMC), or
- Trial Sponsor

9.9 Continuation of Therapy

The allocated intervention will not be administered to a participant outside of the Delivery Room (DR). The allocated intervention must be commenced within 60 seconds of the face mask (or similar) being placed on the face of the infant following birth and must not exceed a maximum of 20 minutes. Any PEEP administered beyond the protocol-defined 20-minute intervention period does not form part of the protocol, and hence, DR data does not need to be collected.

10 OUTCOMES

10.1 Primary Outcome

The primary outcome is the prevalence of the composite outcome of either death or BPD at 36 weeks PMA as assessed by standard oxygen reduction test [44]. To be consistent with other neonatal respiratory trials BPD will be reported as a dichotomous outcome [26, 33].

10.2 Secondary Outcome(s)

We will capture **32 secondary outcome measures**, these include all the initial DR resuscitation, short-term respiratory morbidity and potential harm secondary outcomes used in the SAIL Trial [33]. The **eleven (11) principal secondary outcomes** include:

1. Individual components of primary outcome (death or BPD) at 36-week corrected PMA
2. Failure of non-invasive ventilation in first 72 hours
3. Death in first 10 days of life
4. Oxygen requirement ≥50% for 3 or more consecutive hours in first 72 hours
5. Surfactant therapy in first 72 hours
6. Air leak and/or pulmonary interstitial emphysema (defined on chest radiograph; CXR or lung ultrasound) in the first 10 days of life
7. Patent ductus arteriosus requiring therapy in first 72 hours
8. Intraventricular haemorrhage (grade 3 and 4) (defined via imaging) by day 10 of life
9. Intubation during the intervention period (up to the first 20 minutes after commencing respiratory support following birth)
10. Meeting the protocol criteria for failure of non-invasive ventilation during the intervention period (up to the first 20 minutes after commencing respiratory support following birth) (refer to Table 7.2)
11. Grade of BPD[45]

Additional Secondary Outcomes:

- <u>Initial DR Resuscitation:</u>
  1. Lowest and highest Heart Rate in the DR as recorded for up to first 20 minutes of intervention (from minutely heart rate profile)
  2. Highest oxygen requirement in the DR as recorded for up to first 20 minutes of intervention
  3. Maximum positive inspiratory pressure (PIP) used in DR as recorded for up to first 20 minutes of intervention
  4. Maximum PEEP used in the DR as recorded for up to first 20 minutes of intervention
  5. Chest drain placed in the DR as recorded for up to first 20 minutes intervention
  6. Lowest and highest SpO_2 in the DR (from minutely SpO_2 profile); taken within the Delivery Room as recorded for up to first 20 minutes of intervention
  7. Highest modified oxygenation index (SpO_2/FiO_2) As recorded for up to first 20 minutes of intervention

- First 10 days of Life in the NICU:
  1. Use of inotropes
  2. Supplemental oxygen use: FiO_2 at24 hours after birth, 72 hours, and midday on 7 and 10 days after birth
  3. Highest PEEP used during non-invasive ventilation in the NICU during the first 72 hours after birth, and also PEEP at 24 hours, 72 hours and at midday on 7 and 10 days after birth
  4. Need for invasive mechanical ventilation at 7 and 10 days.

- Hospital Stay*:
  1. Retinopathy of prematurity (stage 3 or higher or requiring treatment) at or before 36-week corrected PMA
  2. Significant brain injury (IVH grade 3 or 4, periventricular leukomalacia) at or before 36-week corrected PMA
  3. Pneumothorax and pulmonary interstitial emphysema
  4. Duration of all respiratory support (ventilation and non-invasive support)
  5. Duration of invasive respiratory support
  6. Duration of non-invasive support
  7. Use of postnatal steroids for treatment of BPD
  8. Death during hospital stay*
  9. Length of hospital stay*
  10. Oxygen requirement at discharge to home.

**Hospital Stay relates to initial admission for management of prematurity. This may include admission at more than one hospital as long as an infant is directly transferred between hospitals and not first discharged home.*

In addition. The following long-term secondary outcome measures will be captured at two-year follow up:

- 24 Months Corrected GA:
  1. Death
  2. General gross motor ability
  3. General cognitive ability
  4. Visual impairment or blindness
  5. Hearing impairment of deafness
  6. Duration of supplementary oxygen therapy after discharge (if applicable)
  7. Hospital admission for a respiratory cause.

11 SAFETY MONITORING AND REPORTING

Safety and adverse events will be monitored during the study to ensure timely detection of events that may affect safety or continued participation. In this study, an adverse event (AE) is any untoward medical occurrence in an infant who has undergone protocol intervention, and which does not necessarily have to have a causal relationship with the protocol specified intervention. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with a protocol specific intervention, whether or not related to the intervention.

11.1 Definitions

For this study, the following safety definitions will be observed:

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial participant administered an intervention and does not necessarily have a causal relationship with this intervention.

Related Adverse Event (AEs): An adverse event that is judged as having a reasonable causal relationship with the trial intervention.

Note: The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE): Adverse events are considered 'serious' if they threaten life or function. Due to the significant information they provide, SAEs require expedited reporting. SAEs are defined as any adverse event which:

- Results in death
- Is life threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect; or
- Other significant medical event*

Note: Life-threatening refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

**Medical and scientific judgement should be exercised in deciding whether an adverse event should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in this definition should also be considered serious.*

Unexpected and Related Serious Adverse Event (URSAE): An adverse event that is:

- Serious – meets the definition of an SAE (see above)
- Related – resulted from administration of the trial intervention
- Unexpected – the event is not described in the protocol as an expected occurrence

11.2 Specific Protocol-Defined Adverse Events and Serious Adverse Events

The POLAR Trial population involves critically ill preterm infants that are anticipated to have a high number of AEs and SAEs. Therefore, **the protocol has designated study-specific AEs and SAEs that are required to be reported within a certain timeframe.**

Table 11.1 below lists specific protocol-defined AEs and the time frame in which they are to be reported within.

Table 11.1: Specific Protocol-Defined AEs:

Adverse Event Definition	Reporting Time Frame
Oxygen requirement of FiO_2 ≥50% for 3 hours or more	Within the **first 72 hours** of life
Infant requiring FiO_2 >30% or mechanical respiratory support using an endotracheal tube	Respiratory support assessment only at **day of life 28.**

The above AEs occurring in each specified time frame are to be recorded on the Adverse Event Form within the POLAR REDCap Data Management System (DMS). In addition, if any of the above protocol-

defined AEs occur beyond the specified reporting time frame, they are also to be recorded and entered in the Data Management System, only if deemed **related or possibly** related to the study intervention, as assessed by the Site Investigator.

Any additional adverse events deemed **related or possibly related** to study intervention, as evaluated by the site Principal Investigator, should also be documented on the AE form, and entered in the Data Management System.

Table 11.2 below lists specific protocol defined SAE/URSAEs and the time frame in which they are to be reported within.

Table 11.2. Specific Protocol-Defined SAE/URSAEs

Serious Adverse Event Definition	Reporting Time Frame
Any Death	Within the **first 72 hours** of life
Pulmonary Haemorrhage	Within the **first 72 hours** of life
Grade 3 or 4 IVH and/or PVL	Head ultrasound findings within the **first 10 days of life** (report based only).
Pneumothorax and/or pneumopericardium. These will be supplemented by data on: a) Any chest tube b) Need for new chest tube after arrival in NICU	Radiographic or lung ultrasound evidence within the **first 10 days of life.**
Administration of epinephrine or use of chest compressions.	Within the **first 72 hours** of life

Note: Death is a component of the composite primary outcome of the POLAR trial and also an outcome of a SAE. The purpose of reporting any death in the first 72 hours as a SAE is to allow causality (See Section 11.5) and expectedness (See Section 11.7) to be fully investigated by the Medical Monitors. Stillbirths are not required to be reported as SAEs.

In addition, should any of the above protocol-defined SAEs occur beyond the specified reporting time frame, they must also be documented on the AE Form and entered into the POLAR REDCap Data Management System (DMS), only if deemed **related or possibly** related to the study intervention.

An Expedited Safety (SAE) Report Form must also be completed and submitted to the Sponsor within 24 hours of becoming aware of any protocol-defined SAE/URSAE. Refer to Section 11.3 below for further details on reporting SAEs/URSAEs to the Sponsor.

An Investigator Expedited Safety (SAE) Report Form is not required when a protocol-defined SAE occurs outside of the specified reporting time frame.

11.3 Safety Issues Requiring Expedited Reporting

The following definitions describe additional safety events that require expedited reporting to stakeholders including the Sponsor-Investigator, Investigators, HRECs/IRBs, local governance offices, the TGA and Competent Authorities/Regulatory Agencies, as per your local country-specific laws and regulations.

Significant Safety Issue (SSI): A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. An SSI is a new safety

issue or validated signal considered by the Sponsor in relation to the intervention that requires urgent attention of stakeholders. This may be because of the seriousness and potential impact on the benefit-risk balance of the intervention, which could prompt regulatory action and/or changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the intervention.

Urgent Safety Measure (USM): A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This is a type of SSI that can be instigated by either the Investigator or Sponsor and can be implemented before seeking approval from HRECs/IRBs, Competent Authorities/Regulatory Agencies, or institutions.

11.4 Assessing the Seriousness of a Participant's AE

The seriousness of an AE will be assessed by an Investigator according to the definition of a Serious Adverse Event (SAE) in Section 11.1, with the following exception:

- Hospitalisation/extended hospitalisation due to progression of clinical condition will not be considered an SAE for the purposes of this study.

11.5 Assessing the Relatedness (Causality) of a Participant's AE

All adverse events/serious adverse events must have their relationship to the trial intervention assessed by the Site Principal Investigator who evaluates the adverse event based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the intervention should always be suspected.

The relationship of the event to the trial intervention will be assessed as follows:

Code	Causal Relationship		Description
1	Unrelated	Unrelated	The AE is clearly NOT related to the intervention
2	Unlikely		The AE is doubtfully related to the intervention
3	Possible	Related	The AE may be related to the intervention
4	Probable		The AE is likely related to the intervention
5	Definite		The AE is clearly related to the intervention

Preterm birth and subsequent NICU care are associated with many risks including severe morbidity and mortality. Many of these risks overlap with events that would or could be an AE/SAE/SSI due to the trial intervention. Death is also a primary outcome of the POLAR Trial. In the SAIL Trial, death within the first 48 hours after birth was found to be higher in the intervention group. The SAIL Trial did not have a detailed method of classifying death, complicating the interpretation of this finding. Consequently, the POLAR Trial will aim to classify the cause and expectedness of each reported death using the above categories, as well as specific diagnostic information within the CRF. If required, the DSMC, Trial Medical Monitors, or Trial Coordinator will contact the reporting Site Principal Investigator to request further clinical information, for example de-identified/redacted post-mortem, mortality/morbidity review reports or other investigations, that aid in ascertaining the causation and expectedness of death.

11.6 Assessing the Severity of a Participant's AE

The Site Principal Investigator will be responsible for assessing the severity of an adverse event (AE). The determination of severity for all adverse events should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade	Severity	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL
Grade 4	Life Threatening	Life-threatening consequences: urgent intervention indicated
Grade 5	Fatal	Death related to AE

11.7 Assessing the Expectedness of SAEs

An SAE that is deemed to be related to the trial intervention must be assessed to determine whether the event is expected or unexpected in terms of the current known safety profile of the intervention. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the trial intervention.

Expected adverse reactions are AEs that are known to occur for the trial intervention being studied. Expectedness is assessed based on the awareness of AEs/SAEs previously observed, not on the basis of what might be anticipated from the properties of the trial intervention.

It is the responsibility of the POLAR Medical Monitors to assess expectedness of all reported SAEs for the trial.

11.8 Documentations of AEs

For the purposes of this study, the Site Principal Investigator is responsible for recording all adverse events, with the following exceptions:

- Conditions that are present at screening and do not deteriorate will not be considered adverse events.

The description of each adverse event (AE) on the CRF will include:

- A description of the AE
- The onset date, duration, date of resolution
- Severity (mild, moderate, severe, life threatening or fatal)
- Seriousness (i.e., is it an SAE/does it meet the definition of an SAE?)
- Any action taken, (e.g., none, intervention ceased/delayed, any treatment given, follow-up tests administered)
- The outcome (i.e. recovering/resolving, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, fatal, unknown)

- The likelihood of the relationship of the AE to the study intervention (Unrelated, Unlikely to be related, Possibly related, Probably related, Definitely related).

Changes in the severity of an AE will be reported as separate events. AEs characterised as intermittent will be documented for each episode. All AEs will be followed to adequate resolution, where possible.

Please refer to the POLAR Manual of Procedures (MoP) document for further details on how to record adverse events.

11.9 Capturing and Eliciting Adverse Event/Reaction Information

11.9.1 Adverse Event Reporting

All Adverse events and adverse reactions must be recorded from the time the participant is randomised until 48 hours after the study primary endpoint (i.e., 36 weeks post PMA).

The specific protocol-defined AEs (refer to Table 11.1 and 11.2) occurring in each specified time frame are to be recorded on the Adverse Event (AE) CRF within the POLAR study Data Management System (DMS). In addition, if any of the protocol-defined AEs occur beyond the specified time frame, they must also be recorded and entered in the POLAR Data Management System (DMS).

Any additional adverse events deemed related or possibly related to study intervention, as evaluated by the Site Investigator/s, should also be documented, and entered in the POLAR Data Management System (DMS).

11.9.2 Serious Adverse Event Reporting

Site Principal Investigator Reporting Procedures:

The Site Principal Investigator/delegate is responsible for recording all safety events in the source document. The Site Principal Investigator is responsible for expedited reporting of the following local safety events:

1. USMs
2. All SAEs

USMs and SAEs must be submitted to the Sponsor c/o the Trial Coordinating Centre at MCTC, as soon as possible (but within 24 hours of the first knowledge of the event), using the POLAR Expedited Safety Report Form.

For Australian sites only, the Site Principal Investigator, or delegate, is also responsible for reporting SSIs, local USMs and local URSAEs to their Research Governance Office (RGO) within 72 hours of becoming aware of the event and in accordance with their local governance authorisation, if applicable.

For international sites, the Site Principal Investigator, or delegate, is responsible for reporting local SSIs, USMs and URSAEs to their institutional review board/ethics committee, as per local regulations.

SAEs and USMs that occur from the time a participant has signed the informed consent form or is randomised (in situations of deferred consent), until 48 hours after the study primary endpoint (i.e. 36 weeks post PMA), must be reported within 24 hours of becoming aware of the event, in accordance with the reporting timeframes outlined in Section 11.2 above.

The Site Principal Investigator must:

- Determine whether an AE is 'Serious' i.e., meets the definition of an SAE (refer to section 11.1)
- For SAEs, the Site Principal Investigator must then ascertain the suspected cause

- The relatedness (attribution) to the SAE must be recorded in the patients' medical records and reported on the POLAR Expedited Safety (SAE) Report form.

SAEs, including USMs, must be reported by completing the POLAR Expedited Safety (SAE) Report form and emailing completed and signed forms to the following:

Report To:		Email To:
Sponsor c/o MCRI	Trial Coordinating Centre c/o Melbourne Children's Trial Centre (MCTC)	safetydesk.mctc@mcri.edu.au

The Site Principal Investigator is ultimately responsible for reporting the SAE and must sign the final Expedited Safety (SAE) Report Form. Should the Principal Investigator not be available to sign the initial SAE report form within the required 24-hour reporting time period, a comment to this effect must be written on the report and the report signed by the clinician attending to the participant at the time and emailed to the Sponsor. The Principal Investigator must sign the SAE Form at the next earliest possible convenience and the SAE Report Form re-sent to the Sponsor.

Table 11.3: Expedited Safety Report Form Submission Guidelines

Initial Report	Within one working day/24 hours of discovery or notification of the event. If the reporting of an SAE is delayed by more than 24 hours, an explanation must be provided.
Incomplete Reports	If all details are not available at the time of the initial report a completed report must be sent within the next 10 days.
Updated Report	If the event is not resolved (or 'on-going') at the time of the initial report, the SAE Form must be submitted every 30 days until the event is resolved, death has occurred or the condition has stabilised. If a change occurs in a stable condition (i.e. either worsens or improves), then a new SAE Form should be emailed.

The Investigator at the participating Site is responsible for determining the local SAE reporting requirements of the responsible Sponsor, HREC/IRB and to Competent Authorities/Regulatory Agencies and subsequently notifying the Sponsor, HRECs/IRBs, Research Governance Offices (if applicable) and Competent Authorities/Regulatory Agencies of SAEs, as required.
All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participants participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilises
- The event returns to baseline if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

<u>Sponsor-Investigator Reporting Procedures:</u>

The Sponsor-Investigator (or Sponsor's delegate) is responsible for:

- Implementing and maintaining a suitable recording system to record information from all SAEs/URSAEs received from participating sites.
- Ensuring that the Sponsor-Investigator is notified of each SAE/URSAE to enable the SAE/URSAE to be assessed by the Sponsor-Investigator and any other appropriate reviewers for nature (expected/unexpected), and causality.
- Reporting AEs to regulatory authorities and ethics committees according to local applicable laws. In addition, URSAEs will be reported to the appropriate regulatory authorities (both national and international) and investigators following local and global guidelines and requirements.
- Considering information provided by (non-serious) adverse event data.
- Informing each participating site of new information arising from serious and non-serious adverse events that may affect the conduct of the Trial, or the rights, interests, safety, or wellbeing of trial patients.
- Providing any updated safety information to all Site Principal Investigators.

The Sponsor-Investigator (or Sponsor's delegate) is also responsible for providing the following additional safety information to the approving HRECs/IRBs and appropriate regulatory authorities:

1. Provide an annual safety report, including a summary of the evolving safety profile of the trial.

12 DATA MANAGEMENT

12.1 Data Collection

All Site Principal Investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Principal Investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs) and source documentation.

12.1.1 Source Data

Source data will be the electronic or paper-based medical record (hospital records, observation charts) for each participant, plus the physiological findings made in the Delivery Room, NICU and/or at BPD assessment, as appropriate. Source data will be entered directly into the appropriate CRF within the POLAR study REDCap Data Management System (DMS) for each participant, or onto the pre-printed paper CRF for collecting data. Paper CRFs are provided in the following instances only:

- Delivery Room Management paper CRF; to allow for real-time recording of physiological parameters captured during the birth. The Delivery Room CRF is designed to provide a practical method of recording key clinical and physiological data points used in the NRP algorithm by the Delivery Room Team 'scribe', in the same format needed to collect relevant data for the POLAR Trial.
- Transfer Pack CRFs; to facilitate data collection from participants transferred to other hospitals prior to their discharge home
- Two-Year Follow-Up paper CRF, to facilitate completion of the follow-up assessment from participants who do not return to their birthing hospital for assessment.

Any data recorded directly on the paper CRFs, for which no other written or electronic record exists, will be considered source data (e.g. participant questionnaires). CRFs and source documents must

always be available for inspection by authorised representatives of the Sponsor and regulatory authorities, such as the TGA or US Food and Drug Administration (FDA).

The Site Principal Investigator is required to maintain a participant identification code list to allow unambiguous identification of each participant included in the trial. This list should contain the participant's full name, data of birth and their Participant Identification Number (PID). This list must be held in confidence at the Principal Investigator's site.

12.1.2 Source Documents Required for Submission for remote Source Data Verification (SDV)

Source documents pertaining to the trial must be maintained by participating sites and de-identified/redacted copies provided to the Data Coordinating Centre (DCCe) in accordance with the POLAR Source Document Plan and Submission Checklist, to enable remote Source Data Verification (SDV).

Remote Source Data Verification (SDV) will be undertaken in accordance with the POLAR Clinical Monitoring Plan (CMP) and observing the European Medicines Agency (EMA) Guidance on the Management of Clinical Trials during the COVID19 (coronavirus) Pandemic; version 5.0, dated: 10/02/2022.

Source documents include a participant's medical records, hospital charts, clinical charts, the participant's shadow files, as well as the results of any diagnostic tests such as chest radiographs, x-rays, lung ultrasounds, CT/MRI scans, laboratory tests, etc.

Please refer to the POLAR Source Document Plan & Submission Checklist and the Manual of Procedures (MoP) Document, for a full list of source documents required for the study.

12.1.3 Data Capture Methods

The Data Coordinating Centre (DCCe) provides a REDCap (Research Data Capture) Data Management System (DMS) for the secure entry and storage of POLAR trial data. REDCap is a secure, web-based application for building and managing online surveys and databases. Access to the POLAR REDCap database will be granted to individual participating site users by the DCCe Data Manager or Central Trial Coordinator.

Participating site clinical teams/research teams will enter trial data directly into the secure POLAR study Data Management System (DMS), with the exception of the Delivery Room (DR) data which will initially be captured on the paper CRF and subsequently entered into the database.

Designated and authorised participating site staff must complete the CRFs and supporting documentation for each participant within a timely manner of each assessment occurring. All staff delegated by the Site Principal Investigator to enter data must be indicated on the Site Signature and Delegation of Authority Log.

12.1.4 Quality Assurance

The Data Coordinating Centre (DCCe) will review completed data for accuracy, completeness, and consistency, whereby requests for corrections and/or clarification of data (e.g., data queries) will be sent to the Principal Investigator or designated participating site staff when inconsistencies are identified during the review process.

All corrections and alterations to CRF data must be addressed by participating sites in a timely manner and according to instructions provided within the POLAR CRF Completion Guidelines. Additions, deletions and/or alteration to data within the CRFs will be recorded in a secure, computer-generated, time-stamped audit trail, including the reason for the change.

Please refer to the POLAR CRF Completion Guidelines for further details regarding data entry and query management.

12.2 Data Storage

Hard copy data/paper documentation will be securely stored by the participating site in a locked cupboard in a secured location. Electronic data will be securely stored on the POLAR REDCap Data Management System (DMS), hosted by MCRI IT Department, Melbourne Australia.

Trial related essential documents maintained for the study will be filed within the POLAR electronic Trial Master File (eTMF) platform, Florence eBinders™, a cloud-based SaaS software maintained by Florence Healthcare, hosted in Germany, EU via Amazon Web-Services (AWS) and backed up daily.

Investigator Site Files (ISF) pertaining to each participating site will also be maintained electronically via the Florence eBinders™ platform by each participating site, to enable remote monitoring of essential trial and regulatory documentation.

Refer to the POLAR Data Management Plan (DMP) for detailed information on data storage.

12.3 Record Retention

All trial-related information will be kept confidential, and only disclosed with parent/guardian permission, or if required by law. Participants will not be identifiable in any publication or presentation of the work.

All trial data will be stored for at least 25 years after the completion of the clinical trial, or until the 25th birthday of the youngest participant, whichever is later. Only the Study Investigators will have access to the trial data. Hard copy data will be stored in a locked cupboard within the Neonatal Research Unit or Melbourne Children's Trial Centre (MCTC) at the MCRI.

Electronic data will be stored in a password protected folder on the Neonatal Research Unit's dedicated server within the MCRI. This server is managed by the MCRI IT and access is via approval from the Neonatal Research Group Leader and Information Technology Department. The server has a seven layer back up and files are backed up daily.

12.4 Archiving of Trial Documents

Trial data and other essential documentation must be retained at participating sites for a period of at least 25 years, or longer, if required by local regulations.

It is the responsibility of the Sponsor-Investigator to inform the Site Principal Investigators and Participating site teams when these documents no longer need to be retained. Trial documents are not permitted to be destroyed without the prior written agreement from the Sponsor-Investigator. Should the Principal Investigators wish to assign the trial records to another party or move them to another location prior to this time, advanced notice must be provided to the Sponsor-Investigator, in writing.

A zipped folder containing a copy of participating sites Investigator Site Files (ISF) maintained electronically via the Sponsor's approved platform, Florence eBinders™, will be provided to each participating site by the TCC at the time of archiving. Participating sites will also have the option of downloading an entire copy of their ISF and storing a copy locally on institutional servers.

13 STUDY OVERSIGHT

13.1 Governance Structure

The organisational and governance structure is summarised in Figure 7. The POLAR Trial Research Network will form the Trial Steering Committee (TSC). This consists of the 15 Chief and Associate Investigators across ten sites in Australia, North America, and Europe involved in the MRFF Grant application, along with a parent representative/consumer.

The TSC with the Trial Statistician will provide the scientific leadership for the study. The Trial Coordinating Centre (TCC) [RWH/MCRI] and the Data Coordinating Centre (DCCe) [Melbourne Children's Trials Centre (MCTC)/Clinical Epidemiology and Biostatistics Unit (CEBU)] based at the MCRI, are collaboratively managing the trial.

The TCC is responsible for clinical leadership, the MCTC is responsible for research operations and overall clinical trial management and the DCCe is responsible for statistical analysis and database management.

The Study Endpoint Adjudication Committee (SEAC) will provide overall mortality monitoring for the study, identifying any mortality safety signals of concern. The SEAC is a sub-committee of the Data and Safety Monitoring Committee (DSMC) and will report any significant safety issues (SSIs) to the Chair of the DSMC.

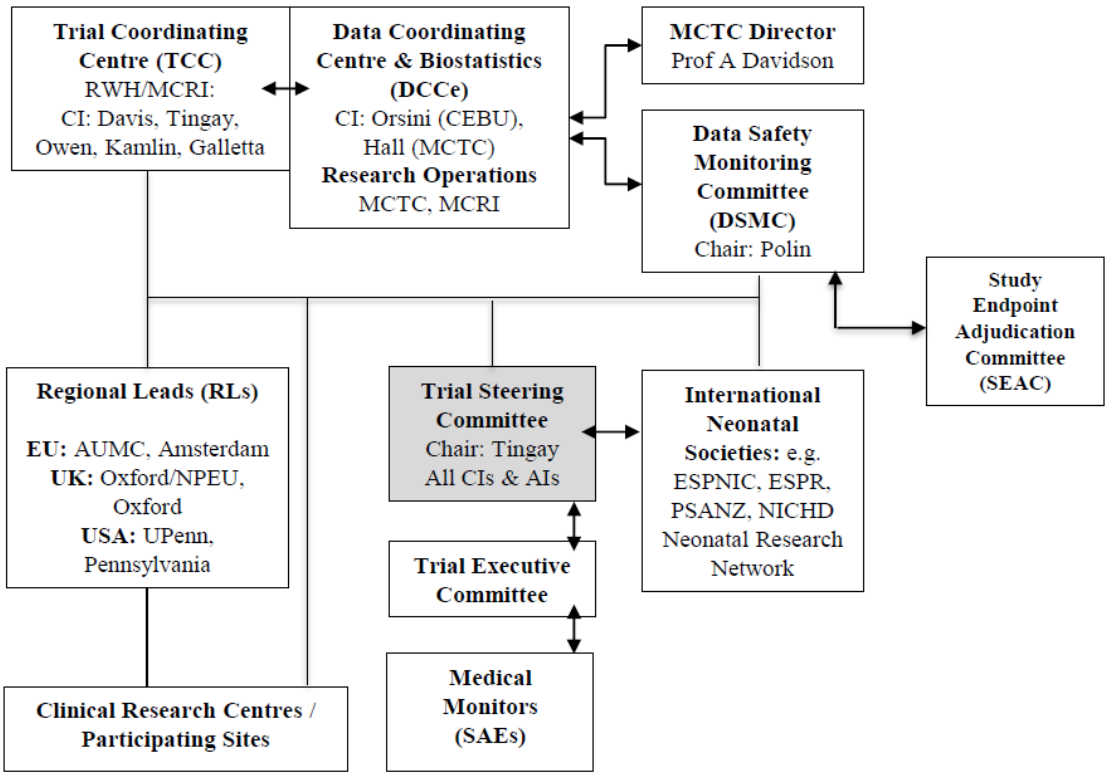
The Medical Monitors will provide overall intervention-vigilance for the study by reviewing all reported SAEs in real-time, determining the expectedness and relatedness of the safety event and the appropriate course of action. If deemed necessary, the Medical Monitors, will report any significant safety issues (SSIs) identified to the Data and Safety Monitoring Committee (DSMC).

The TCC (c/o POLAR Trial Coordinator) will serve as the liaison between the participating sites, the Trial Steering Committee (TSC) and all other committees supporting the study.

13.1.1 POLAR Trial Research Network

The network includes a global collaboration of clinical researchers, triallists and statisticians with a diverse skill set and excellent international standing in the field of neonatal respiratory medicine. The team has an extensive collaborative network and represents the major opinion leaders in our field. Members of the scientific leadership team hold positions in international and regional neonatal academic and strategic organisations, including ILCOR, European Society of Paediatric and Neonatal Intensive Care, European Society of Paediatric Research, Perinatal Society of Australia and New Zealand, Foetal, National Institute of Child Health and Development (NIH) Neonatal Research Network, Newborn Committee of the Canadian Paediatric Society and Canadian Critical Care Trials Group. Members of the team have been involved in large clinical trials that have influenced all aspects of neonatal respiratory care in the last 25 years, including high-frequency ventilation, non-invasive ventilation, oxygen targets, permissive hypercapnia, and DR care.

Figure 7: POLAR Trial Research Network



13.1.2 Trial Coordinating Centre (TCC)

The MCRI/RWH will be the TCC. The TCC will be directed by Prof Tingay, along with Prof Davis, Dr Owen, and Dr Kamlin, with overall trial support and management provided by Ms Laura Galletta. The TCC will function to:

1. Provide leadership in directing the clinical aspects of protocol development and implementation
2. Develop training materials and instructions for the intervention algorithms and other clinical procedures
3. Oversee study governance
4. Oversee the POLAR Trial network of supporting committees
5. Coordinate participating site start-up activities and site staff training and implementation (with each Regional Lead)
6. Coordinate the development and distribution of all aspects of study protocol
7. Overall clinical trial oversight and management

The TCC will employ a Trial Coordinator who will assist in these tasks and work closely with the DCCe Team. A member of the TCC will conduct all site initiation meetings/visits and annual site monitoring visits

13.1.3 Data Coordinating Centre (DCCe)

Under the direction of Ms F Orsini of the Clinical Epidemiology and Biostatistics Unit (CEBU) and Prof A Davidson (Director, Melbourne Children's Trials Centre), the DCCe will support the TCC and research network to assure collaboration across sites, along with standardisation and uniformity of procedures, to yield high-quality data. Specific responsibilities include:

1. Providing statistical leadership data management support for the conduct of the trial
2. Develop and implement the data management and randomisation systems
3. Establish and maintain data collection and entry procedures

4. Train and monitor clinical sites in data collection and data integrity
5. Participate in all study meetings and collaborate with the TCC and TSC in preparation of publications and presentations.

13.1.4 Regional Leads (RLs)

The Amsterdam University Medical Centre, Netherlands (PI: Prof Anton van Kaam), the University of Oxfords National Perinatal Epidemiological Unit (NPEU) Clinical Trials Unit (PI: Prof Charles Roehr), and the Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia, USA (Pis: Prof Haresh Kirpalani and Dr Elizabeth Foglia) will be the principal International Partner Research Organisations for the trial. Each Partner Research Organisations will act as the respective Regional Leads for Europe, the United Kingdom and North America to streamline trial implementation and governance. Each RL will be directly reportable to the TCC based at the MCRI/RWH in Melbourne, AUS. The three International Partner Organisations have an established and independently funded research structure with an outstanding history in leading large influential neonatal trials, including the SAIL and STOP-BPD trials, and a history of collaborating with the TCC.

Each Regional Lead will work under the direct supervision of the TCC and DCCe and be responsible for providing leadership and oversight for the respective region.

13.1.5 Clinical Research Centres / Participating Sites

Each **Site Principal Investigator (PI)** will be responsible for the oversight of the trial locally, ensuring ethical and regulatory approval is obtained prior to commencement, and that the study protocol is adhered to. A local **Research Coordinator** (e.g. Research Nurse or Study Coordinator) or designated **Clinical Care Team Member** (e.g. Sub-Investigator) will be responsible for the coordination of study activities, clinical team training, and implementation of study procedures and data quality standards under the supervision of the Site Principal Investigator, where applicable. Prior to trial implementation, each site must provide the Central Trial Coordinator c/o the TCC with evidence of ethics committee review and approval, completed signature and delegation logs, signed Site Investigator Protocol Signature and Agreement Pages and training logs, amongst other required essential trial documentation. The Site Principal Investigator, and where applicable, the Research Coordinator or designated Clinical Care Team Member, will work closely with the DCCe, TCC and RLs.

Please refer to the POLAR Manual of Operations (MoP), for a full list of essential documents required for the study.

13.1.6 Trial Steering Committee (TSC) Structure

Within the Trial Steering Committee (TSC) there will be a **Trial Executive Committee (TEC)** and a **Trial Steering Committee (TSC).**

The Trial Executive Committee will consist of the trial leadership group (TCC and DCCe) and trial statistician, and be responsible for all scientific, fiscal, and administrative decisions on behalf of the trial.

The Trial Steering Committee will consist of the Regional Leads (RLs) and the secondary leadership group and be responsible for overall trial direction and coordination of subcommittees and taskforces. The Trial Steering Committee membership will consist of the TCC, DCCe and RL members, the listed Chief Investigators (Cis) on the original MRFF grant, and Prof Andrew Davidson (Sponsor Representative, MCRI/MCTC), and liaise directly with international/regional neonatal societies.

The TEC will meet fortnightly during the trial development and site start-up phase of the trial and may reduce to less frequent meetings during the trial conduct and follow-up phases.

The TSC will meet quarterly via videoconference during trial conduct, and where permissible, face-to-face when in attendance at international scientific conferences.

Please refer to the POLAR Trial Steering Committee (TSC) Charter for further details.

13.1.7 Independent Data and Safety Monitoring Committee (DSMC)

An Independent Data Safety Monitoring Committee (DSMC) will be established to review emerging external evidence and monitor protocol compliance, adverse events (Aes)/serious adverse events (SAEs), significant safety issues (SSIs), mortality and progress of recruitment in accordance with the POLAR DSMC Charter.

The TSC will provide the DSMC with a charter. The DSMC will receive both blinded and unblinded interim safety reports and will consist of the following members:

- A team of Clinicians/Neonatologists
- A Neonatal Ethicist
- An Independent Statistician (University of WA)
- Additional members as required.

Refer to the POLAR DSMC Charter for further details.

13.1.8 Study Endpoint Adjudication Committee (SEAC)

A Study Endpoint Adjudication Committee (SEAC) will be established to review, validate, and verify primary endpoint data from de-identified/redacted source documented requested, in order to:

1. Evaluate and classify mortality events
2. Assess whether the death was possibly related to the trial intervention

The SEAC is a sub-committee of the Data Safety Monitoring Committee (DSMC) and will report to the Trial Steering Committee (TSC), as required. Further details are provided in the SEAC Charter document.

The Trial Coordinating Centre will provide the SEAC with a Charter. The SEAC will be blinded to the intervention and consist of the following members:

- A team of independent Clinicians/Neonatologists
- Trial Coordinating Centre (TCC) Representatives.

Refer to the POLAR SEAC Charter for further details.

13.2 Quality Control and Quality Assurance

To standardise the collection of data by Site Principal Investigators and clinical care teams/research teams, training of the Site Principal Investigator and clinical care teams/research teams will be undertaken by the Trial Coordinating Centre (TCC) team. This will include staff familiarisation of the protocol and randomisation procedures, provision of study-specific documentation, SOPs and manuals, attendance at site initiation visits (SIVs) and training on the POLAR web-based Data Management System (DMS), i.e., REDCap.

The Site Principal Investigator and Research Coordinator will train the remaining local site clinical care team, in particular, the senior medical staff conducting consent, randomisation and applying the intervention.

Training of the Site Principal Investigator and Research Coordinator/Study Team will include all aspects of study conduct. The Trial Coordinating Centre (TCC) (or Regional Leads (RLs), if applicable) may conduct annual site visits and audits to monitor protocol compliance (especially in the Delivery Room), governance and reporting accuracy and standards (Quality Assurance and Good Clinical Research Practice). Where on-site monitoring is not possible, risk-based remote monitoring will be undertaken in its place.

All participating trial sites will have access to the POLAR Manual of Procedures (MoP) document and the CRF Completion Guidelines.

13.2.1 Trial Monitoring

Trial monitoring is undertaken to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The Sponsor's monitoring frequency has been determined by an initial risk assessment performed prior to the start of the trial. A detailed Clinical Monitoring Plan (CMP) has been developed detailing the frequency and scope of the monitoring for the trial. Throughout the conduct of the trial, the risk assessment will be reviewed, and the monitoring frequency adjusted, as necessary.

Remote and central monitoring will be conducted for all participating sites. The scope and frequency of monitoring has been determined by the risk assessment and detailed in the Clinical Monitoring Plan (CMP) for the trial. Unresolved or significant findings from remote monitoring visits may result in the escalation from remote visits to on-site visits.

- Regular remote and central monitoring will be performed according to the trial specific Clinical Monitoring Plan (CMP)
- Central monitoring will occur regularly focusing on targeted source data verification of study endpoint, compliance within the Delivery Room, safety, and other key data variables
- Remote monitoring will occur every 6 months focusing on site compliance with ICH-GCP, informed consent and randomisation/recruitment processes and essential document management
- Data will be evaluated for compliance with the protocol requirements and accuracy in relation to source documents as defined in the CMP
- Following written standard operating procedures, the monitors will verify that the clinical trial is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP and the applicable regulatory requirements
- Each participating site will be provided with copies of monitoring reports within 7 days of each remote monitoring visit
- Independent audits may be conducted by the Sponsor or a representative of the Sponsor, to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

14 STATISTICAL METHODS

14.1 Sample Size Estimation

Using data from our neonatal networks[5] we estimate the rate of death/BPD at 36 weeks corrected PMA (primary outcome) in the control group to be 52%. A reduction in death/BPD to 41% would represent a major advance in care for individuals and NICUs, and is consistent with other recent large, randomised control trials with similar populations (e.g. SAIL, SUPPORT, COIN Trials) [5, 26, 33, 36]. A sample size of 430 per group (860 total) will provide 90% power with 2-tailed 0.05 significance level to detect the difference between 41% death/BPD in the intervention group and 52% in the control group (21% RRR and absolute reduction of 11% from the control group). Allowing for 5% drop-out rate, we will recruit 906 infants in total (453 per group).

We anticipate that 1/3 of infants recruited will be in the most vulnerable 23–25-week PMA subgroup. A sample of 155 23–25-week PMA infants per group (310 total) will provide 80% power with 2-tailed 0.05 significance level to detect the difference between 59% death/BPD rate in the intervention group and 74% in the control group (this corresponds to a RRR of 20% and absolute reduction of 15% from the control group). This analysis will be conducted for exploratory purposes.

The sample size for the primary outcome would detect a difference in the important secondary

outcome of failure of non-invasive support (treatment failure) between 52% in the intervention group and 65% in the control group [40] (2-tailed 0.05 significance level) with 97% power. This analysis will be conducted for exploratory purposes.

14.2 Statistical Analysis Plan

The primary analysis of all outcome data will be an intention-to-treat (ITT) analysis including all randomised participants, analysed according to the group they were originally assigned, regardless of what intervention they received, participants' compliance, crossover to other interventions or withdrawal from the study. This approach preserves the prognostic balance in the study groups achieved by randomisation.

14.2.1 Methods of Analysis

For dichotomous outcomes, including the primary outcome, proportions will be compared using the risk ratio and risk difference with 95% confidence interval (CI) obtained from generalized linear models for the binomial family with adjustment for the strata (defined by centre and gestational age category) used in the randomisation. Continuous outcomes will be compared using differences between mean values and 95% CI, estimated from normal linear regression models with the same stratification adjustments. Secondary analyses will use expanded regression models to explore potential confounding effects of chance imbalances between groups in birth weight, gender, antenatal steroids, or mode of delivery. In further secondary analysis, we will explore evidence for heterogeneity of effects between the two gestational age strata, using interaction tests and subgroup analyses, if deemed appropriate.

Subgroup analysis of participants born 23–25-week PMA will be conducted.

The full details for each variable will be included in the POLAR statistical analysis plan (SAP).

14.3 Interim Analyses

An Independent Data Safety Monitoring Committee (DSMC) will be convened four times during the study:

- At recruitment of 50 participants
- At recruitment of 100 participants
- At recruitment of 1/3 of total participants; and
- At recruitment of 2/3 of total participants.

At these four separate occasions the independent DSMC will monitor safety (including number of deaths), data completeness, and general study conduct. Recruitment will not be halted for any of these analyses. Further details of the DSMC analyses are outlined in the POLAR DSMC Charter.

14.4 Early Termination Criteria

The following criteria may cause the trial (one or both groups) to be terminated before the planned target accrual:

- Safety issues including excessive adverse events as assessed by the Data Safety Monitoring Committee (DSMC) or Sponsor
- Inadequate realisation of trial resources, including participant numbers
- Diminished significance of the trial question
- Lost equipoise
- Other evidence that indicates it is unethical to recruit participants to the study.

15 ETHICS AND DISSEMINATION

15.1 Ethics Committee Approval

This protocol and the Informed Consent Form document and any subsequent modifications must be reviewed and approved by a Human Research Ethics Committee (HREC)/Institutional Review Board (IRB) prior to commencing the research. A letter of protocol approval by HREC/IRB will be obtained prior to the commencement of the study, as well as approval for other study documents requiring HREC/IRB approval, from each participating centre.

15.2 Modifications to the Protocol

This study will be conducted in compliance with the current version of the approved protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, study design, participant safety, or may affect a participants' willingness to continue participation in the study is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or Informed Consent Form. All such amendments will be submitted to the HREC/IRB, for approval prior to becoming effective.

15.3 Protocol Deviations

All protocol deviations must be recorded in the participant medical record (source document) and on the corresponding Protocol Deviation CRF in the POLAR Data Management System (DMS).

Protocol deviations will be assessed for significance by the Sponsor-Investigator. Those deviations deemed to have a potential impact on the integrity of the study results, participant safety or the ethical acceptability of the trial will be reported to the HREC/IRB, as per local laws and regulations, within a timely manner. Where deviations to the protocol identify issues for protocol review, the protocol will be amended as per Section 15.2.

For Australian sites only, the Site Principal Investigator, or delegate, is responsible for reporting protocol deviations and/or suspected serious breaches to their research governance office within 72 hours of becoming aware of the event and in accordance with their local governance authorisation, if applicable.

For international sites, the Site Principal Investigator, or delegate, is responsible for reporting protocol deviations and/or suspected serious breaches to their institutional review board/ethics committee, as per local regulations.

The Site Principal Investigator must categorise protocol deviations within the POLAR Data Management System (DMS) as either minor or major according to the following definitions:

Minor Deviations:

A minor protocol deviation is defined as less serious accidental or unintended protocol non-compliance with the HREC/IRB approved protocol, which either:

- Does not significantly impact on the participants' rights, safety, or well-being; and/or
- Does not affect the participant's willingness to participate in the trial; and/or
- Does not significantly impact on the completeness, accuracy, reliability, and integrity of the trial data.

Major Deviations:

Major protocol deviations and protocol non-compliance is defined as accidental or unintended changes to, or serious non-compliance with the HREC/IRB approved protocol which either:

- Significantly effects the participant's rights, safety and/or well-being; and/or
- Impacts on the integrity of the trial's data and/or efficacy/safety assessment; and/or
- Increases the risk or decreases the benefit off the trial,

such that the participant would be excluded from the trial's efficacy and/or safety analysis or would provoke discontinuation from the trial.

Any failure to follow a major component of the protocol will result in a protocol deviation. Examples of a **major** protocol deviations include:

- Failure to follow randomised treatment group assignment in delivery room resuscitation of enrolled infant
- Opening more than one randomisation envelope for an enrolled infant
- Opening the wrong randomisation envelope for an enrolled infant, i.e., open envelope from the wrong stratum or not opening the envelope with the smallest randomisation number in the sequence
- Enrolment and randomisation of an infant who is ineligible for the study
- Failure to follow the approved study protocol that affects participant safety or data integrity
- Failure to report serious adverse event (SAE) or unexpected and related serious adverse event (URSAE) to the Sponsor/TCC
- Continuing research activities after HREC/IRB approval has expired.

15.3.1 Expedited Reporting of Major Protocol Deviations

Major protocol deviations must be reported to the Sponsor within **24 hours** of site staff becoming aware of the event, by completing the POLAR Event of Non-Compliance Report Form and emailing completed and signed forms to the following:

Report To:		Email To:
Sponsor c/o MCRI	Trial Coordinating Centre c/o Melbourne Children's Trial Centre (MCTC)	POLAR@mcri.edu.au

The Site Principal Investigator is ultimately responsible for reporting the major deviation and must sign the final Event of Non-Compliance Report Form.

Should the Principal Investigator not be available to sign the initial Non-Compliance Report form within the required 24-hour reporting time period, a comment to this effect must be written on the report and the report signed by the clinician attending to the participant at the time and emailed to the Sponsor.

The Principal Investigator must sign the Event of Non-Compliance Report Form at the next earliest possible convenience and the Event of Non-Compliance Report Form re-sent to the Sponsor.

Refer to the POLAR Manual of Procedures (MoP) for a full list of protocol deviations for the trial and instructions on reporting protocol deviations to the Sponsor.

15.4 Confidentiality Regarding Trial Participants

The study will comply with the EU General Data Protection Regulation (GDPR) and Data Protection Act 2018 in its current form, which requires data to be de-identified as soon as it is practical to do so.

Participant confidentiality is strictly held in trust by the participating Site Principal Investigators, Research Staff, and the sponsoring institution and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Site Principal Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The participating site will permit access to such records.

All participant discharge summaries, investigative reports and other source documents that leave the site will be de-identified/redacted, "marked" as containing PHI (Protected Health Information) and identified only by the Participant Identification Number (PID#) in order to maintain participant confidentiality. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by Site Monitors, HREC/IRBs or Competent Authorities/Regulatory Agencies.

15.5 Participant Reimbursement

There is no participant reimbursement for the POLAR Trial.

15.6 Financial Disclosure and Conflicts of Interest

There are no financial or other competing interests for Investigators for the overall trial and each study site.

15.7 Dissemination and Translation Plan

The Trial Coordinating Centre (TCC) and/or Data Coordinating Centre (DCCe) will distribute trial information to participating sites via the following tools:

1. POLAR Trial website (www.POLARtrial.org.au)
2. Distribution Lists / Email Correspondence
3. POLAR Trial REDCap Data Management System (DMS) help desk at the MCTC (POLAR@mcri.edu.au); and
4. Direct access to the TCC and RL members.

In addition, a POLAR Trial newsletter for participating centres and their families will be disseminated on a regular basis via the POLAR website (www.POLARTrial.org.au). At study completion, a summary of the trial results will also be made available to all participants and their families via the POLAR website.

15.7.1 Data Sharing Plan

The trial recognises the value of open data sharing and adherence to data sharing principles that align with applicable laws, regulations, and ethical guidelines, therefore, anonymised data from this clinical trial will be made available via a controlled access data sharing mechanism. Interested researchers may request access to the data by submitting a formal data sharing request to the Sponsor. The request will be reviewed by the Sponsor and the Sponsor-Investigator, and any relevant MCRI data sharing committee, considering factors such as scientific merit, data security, and adherence to the approved research objectives.

The anonymised data set collected for the analysis of the POLAR trial will be made available six (6) months after publication of the primary outcome. The study protocol, statistical analysis plan (SAP) and

informed consent forms will also be available. The data may be obtained from the Sponsor, the Murdoch Children's Research Institute, by emailing MCTC@mcri.edu.au.

15.7.2 Publication Policy

All POLAR Trial manuscripts and abstracts ("publications") must, before submission, be reviewed by the POLAR Steering Committee (TSC). The Steering Committee will form the writing committee of the main primary paper. The author line must conclude with "and the POLAR Trial Investigators," and MRFF funding must be acknowledged, specifying the grant number if applicable.

Note: "publications" include abstracts and posters for presentation at national and international meetings.

Manuscripts are assigned a primary reviewer(s) from the Trial Steering Committee who is responsible for final approval. The manuscript is returned to the lead author with major comments (required changes) and minor comments (recommended changes). If there are required changes, the manuscript must be revised and resubmitted for further review. This process is repeated until no required changes remain. In case of persistent disagreement between authors and reviewers, final judgment rests with the Trial Steering Committee chair. Abstracts undergo a similar but abbreviated review.

Additionally, if the analysis is done at the local site: the lead author is required to submit the analytical plan and computer code used to produce the results in the publication from the original dataset. If results cannot be reproduced, the publication will not be approved for submission.

No ancillary study can be published until the primary paper(s) are published.

15.7.3 Authorship

POLAR supports and subscribes to the policies of the International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org). These Requirements state:

> *"Authorship credit should be based on:*
>
> *1) Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data*
>
> *2) Drafting the article or revising it critically for important intellectual content; and*
>
> *3) Final approval of the version to be published.*
>
> *Authors should meet conditions 1, 2, and 3."*

For the purposes of reporting results, POLAR will consider substantial contributions to participant accrual as meeting criterion #1; as accrual is critical for the "acquisition of data".

In general, authors will be named as individuals with as many authors included as permitted by the intended journal. Situations may exist where it is more appropriate to have authors named under an umbrella term. In these situations, a Writing Committee will be named and will include members of the POLAR Trial Investigators. If permitted, authorship will start with the members of the Trial Steering Committee and then work through collaborating center Principal Investigators in order of number of enrolled and randomized infants. Additional authorship positions will be determined by POLAR site accrual. When a site has contributed a large percentage of accrual, additional authors from that center may be selected after approval by the POLAR TSC. The additional authors will be determined by the site Principal Investigator.

When appropriate for unusual contribution, POLAR research staff will be considered for inclusion as other contributing authors. Examples include the TCC Trial Manager and, for papers with detailed statistical analysis, the trial statistician. The life span of POLAR may mean that sustained involvement by a single Trial Manager is not possible. In these circumstances, all staff with direct project-specific responsibilities will be included in the Acknowledgements.

Where journal policies permit, all Investigators who played a contributing role in the study, including to its accrual, will be included in an Acknowledgement section. TCC/DCCe and site staff with direct project-specific responsibilities will also be acknowledged.

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