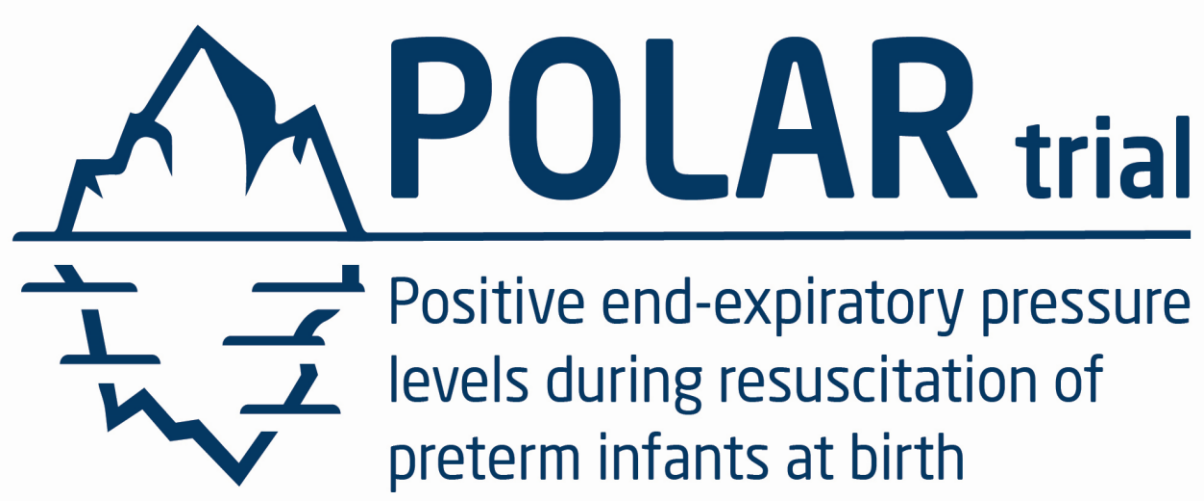

The POLAR Trial:

Positive End-Expiratory Pressure (PEEP) Levels during Resuscitation of Preterm Infants at Birth

MANUAL OF PROCEDURES (MOP)

Version 6.0 – Dated: 26 February 2024

Sponsor-Investigator: Prof David Tingay david.tingay@rch.org.au
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Prepared by the Murdoch Children's Research Institute, Melbourne Children's Trial Centre (MCTC), POLAR Data Coordinating Centre.

CONTENTS

REVISION HISTORY

Version No.	Date	Summary of Changes
1.0	09 March 2021	Initial version
2.0	16 April 2021	- Update to the structure of Screening IDs, as assigned by the POLAR Screening Database (Section 6.2.1). - Update to Section 5.1; Training on PEEP Delivery and training attestation requirements for clinicians delivering the intervention; i.e. "Reading the relevant section/s of the POLAR Protocol relating to your trial-related duties and/or functions, as applicable" (updated from Read the POLAR Protocol).
3.0	11 August 2021	- Updated the Participating Sites/Clinical Research Centres participating in the trial (Section 3.8). - Updated instructions on how to access the POLAR Trial Training Videos (Section 5.2). - Minor corrections and clarifications throughout the manual.
4.0	15 October 2021	- Updated the Participating Sites/Clinical Research Centres participating in the trial (Section 3.8). - Updated Section 5.7 – documents required prior to site initiation meeting. - Added details around parent education video (Section 6.3). - Minor updates to Section 11 – Safety Reporting, to further clarify the safety reporting requirements for the trial. - Minor corrections and clarifications throughout the manual.
5.0	04 July 2022	- Updated the Participating Sites/Clinical Research Centres participating in the trial (Section 3.8) - Added details around Additional parent education video in other languages i.e., Italian and French (Section 6.3) - Minor corrections and clarifications throughout the manual; i.e. Sections 4.4, 5.3 and 8.7.
6.0	26 February 2024	- Update to Section 3.0: Study Organisation / Research Network, to include reference to the Study Endpoint Adjudication Committee (SEAC). - Update to Section 3.8: Participating Sites/Clinical Research Centres; to include complete list of participating trial sites. - Update to Section 6.3: POLAR Parent Education Video; to include reference to Spanish and Polish parent videos. - Additional Section added; Section 6.4.1: Tracking Antenatal Consent Status. - Update to Section 6.5.1: Retention and Use of SAE Data from Participants who deny Consent, to clarify use of safety data when deferred consent is not obtained. - Update to Section 7.2: Participant Withdrawal of Consent, to clarify instances of study withdrawal. - Addition of Section 7.5: Site Participant Randomisation Log, to outline requirements for maintaining listing of enrolled participants - Update to Section 9.1: Study Timeline and Schedule of Assessments (schedule of assessments table) - Update to Schedule 10.6: BPD Assessment at 36-week PMA, to clarify timing of assessment. - Update to Section 10.7: Follow-Up Assessment at 24-Month, to include acceptable methods of follow-up

1.0 Introduction

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

Specifically, the trial will determine whether the use of a high, dynamic PEEP level strategy to support the lung during stabilisation ('resuscitation') at birth, is superior compared with the current practice of a static PEEP level, and hence, reduce the rate of death or bronchopulmonary dysplasia (BPD).

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 standard, static PEEP.

The primary outcome is a lower rate of the combined endpoint of death or BPD (using a standardized oxygen reduction test) at 36 weeks PMA.

A total of 906 infants will be recruited:

- 453 within the Static group; and
- 453 within the Dynamic group.

The study will also compare which has the lower rate of other important secondary outcomes including rates of neurodevelopmental impairment at 24 months of corrected age in survivors.

The trial is being conducted globally across approximately 25 sites within Australia, Europe, the United States, and the UK. The Melbourne Children's Trial Centre (MCTC) based at the Murdoch Children's Research Centre (MCRI) [Melb, AUS] serves as the Central Trial Coordinating Centre (TCC) and Data Coordinating Center (DCCe).

Funding for the study is provided by the Medical Research Future Fund (MRFF, Australian Government) International Clinical Trials Collaborations Grant #1170957.

2.0 Trial Registration

The POLAR Trial is registered on Clinical Trials.gov and the ANZCTR clinical trial registries:

- Clinical Trials.gov (http://www.clinicaltrials.gov) registration number: NCT04372953
- ANZCTR Registry (https://www.anzctr.org.au/) registration number: ACTRN12618001686291

3.0 Study Organisation / Research Network

3.1 Study Sponsor

The study is sponsored by the Murdoch Children's Research Centre (MCRI) [Melbourne AUS]. The Sponsor-Investigator, Prof David Tingay and MCTC Director, Prof Andrew Davidson, will provide overall scientific and administrative oversight for the trial.

3.2 Trial Steering Committee (TSC) with reference to Executive Committee

The scientific leadership group for the study is comprised of 15 Chief and Associate Investigators (AIs) across sites based in Australia, North America, Europe and the United Kingdom, as well as a parent representative. This group will also form the Trial Steering Committee (TSC). Within the Trial Steering Committee (TSC), there will be an Executive Committee. The Executive Committee will consist of the trial leadership group (Trial Coordinating Centre and Regional Leads) and the trial statistician, and be responsible for all scientific, fiscal, and administrative decisions on behalf of the trial.

The Trial Steering Committee will be responsible for:

1. Answering inclusion and exclusion questions from participating sites and study teams
2. Coordinating with other personnel on the study to ensure that information is consistent
3. Addressing safety issues across the study from participating sites and the study team.

3.3 International Trial Coordinating Centre (TCC)

The trial is managed collaboratively by the International Trial Coordinating Center (TCC) and the Data Coordinating Center (DCCe) both based at the Murdoch Children's Research Institute (MCRI), Melbourne Australia.

The Trial Coordinating Center (TCC) is responsible for clinical leadership and its functions include:

1. To provide leadership in directing the clinical aspects of protocol development and implementation
2. To develop training materials and instructions for the intervention algorithms and other clinical procedures
3. To oversee study governance
4. To oversee the POLAR Trial network of supporting committees
5. To coordinate clinical site staff training and implementation (with each Regional Lead).
6. To coordinate the development and distribution of all aspects of study protocol
7. Overall clinical trial oversight and management and participating trial site management.

3.4 Data Coordinating Centre (DCCe)

The Data Coordinating Center (DCCe) is responsible for research operations and supporting the TCC and research network to assure collaboration across sites, along with standardisation and uniformity of procedures, to yield high-quality data. The DCCe will serve as the liaison between the clinical sites, the scientific leadership and the DSMC.

3.5 Regional Leads (RLs)

The Amsterdam University Medical Centres (AMC), Netherlands (PI: Prof Anton van Kaam), the University of Oxfords National Perinatal Epidemiological Unit (PI: Prof Roehr), and the Hospital of the University of Pennsylvania (HUP), USA (PI: A/Prof Elizabeth Foglia) will be the principal International Partner Research Organisations for the trial.

The three institutes will act as the respective Regional Lead (RL)/National Coordinating Centre (NCC) for the Netherlands, the United Kingdom, and North America to streamline implementation and governance within each region. Each PI within each region will also provide real-time clinical support to participating sites to account for the variation in time zones globally.

Each RL/NCC will work under the direct supervision of the TCC and DCCe and be responsible for providing leadership and oversight for their respective region. Each RL/NCC will have a dedicated Clinical Research Coordinator (CRC) to assist with local regulatory, ethics, trial implementation, protocol compliance issues (including non-English languages) and site issues.

Additional Regional Leads will be identified in other European Countries as required.

3.6 Data Safety Monitoring Committee (DSMC)

An independent DSMC acts to monitor and assess study safety and to review emerging external evidence and monitor protocol compliance and progress of recruitment in accordance with the DSMC Charter. Specific responsibilities of the DSMC include:

- Conducting in-depth reviews of the progress of the study at established intervals which includes evaluating participant accrual and follow-up, data quality and monitoring, and adverse events
- Make recommendations regarding continuation, modification, or early termination of the study should it become necessary to protect the safety and welfare of the participants.

3.7 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.

3.7 Medical Monitors

Medical monitors provide medical expertise for trial oversight and safety concerns for the entire clinical trial, from initial study design through final study close-out.

The nominated Medical Monitors (MM) for this study are indicated as follows:

Primary Medical Monitor:	Dr Nicholas Evans	nicholas.evans@sydney.edu.au
Back-Up Medical Monitor:	Dr Douglas Blank	douglas.blank@monashhealth.org
Back-Up Medical Monitor:	Dr David Stewart	david.stewart@rch.org.au

Medical monitors ensure the clinical integrity of the trial participants and provide safety accountability across the duration of the study, while acting as expert safety points of reference for both participating sites and study team members.

Specific responsibilities of the Medical Monitors include:

1. Reviewing all SAEs within 24 hours of receipt and determining the expectedness and relatedness of the event
2. Reporting any significant intervention-related SAEs to the DSMC immediately, if deemed necessary
3. Reporting any significant safety issues identified to the DSMC immediately, if deemed necessary.

Figure 1 below depicts the research network.

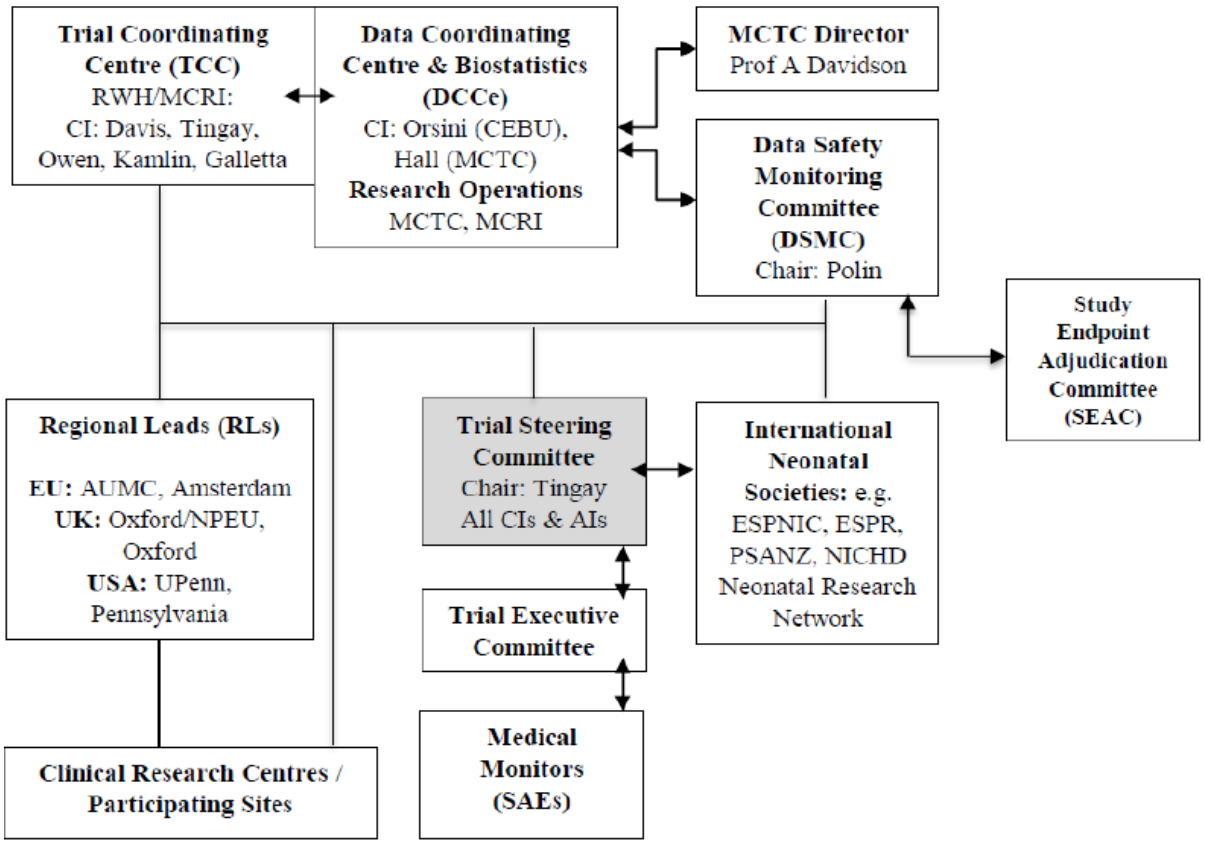


Figure 1: POLAR Trial Research Network

3.8 Participating Sites/Clinical Research Centres

Each participating site/clinical research centre that is activated for screening and enrolling of infants will be assigned a Site ID, which also forms part of the Participant Identification Number (PID#). Site IDs are assigned by the Data Coordinating Centre (DDCe).

Table 1 below provides a list of the participating sites and their corresponding Site ID as confirmed at the time of finalisation of this document. As additional sites are confirmed, this manual will be updated accordingly.

Table 1: Participating Sites/Centres

	Participating Site/Centre	Site ID	Site PI	Location
Confirmed Participation				
AUSTRALIAN SITES				
1	Royal Women's Hospital (VIC)	RWH	A/Prof Louise Owen	Melbourne, VIC
2	King Edward Memorial Hospital	KEMH	A/Prof Andy Gill	Perth, WA
3	Mater Mothers Hospital	MMH	Prof Helen Liley	Brisbane, QLD
4	Women and Children's Hospital Adelaide	WCHN	Dr Chad Andersen and A/Prof Michael Stark	Adelaide, SA
5	Western Health - Sunshine Hospital - Joan Kirner	JKWC	Dr Arun Sett	Sunshine, VIC
EUROPEAN SITES				
6	Amsterdam University Medical Centre	AMC	Prof Anton van Kaam	Amsterdam, NL, EU
7	Radboudumc Amalia Children's Hospital	ACH	Prof Willem de Boode	Nijmegen NL, EU
8	Maxima Medical Centre	MAX	Dr Hendrik Niemarkt	Veldhoven, NL, EU
9	Vittore Buzzi Children's Hospital	ODB	Prof Gianluca Lista	Milan, IT, EU
10	Ospedale Maggiore Policlinico	MAG	Dr Anna Lavizzari	Milan, IT, EU
11	Gemelli University Hospital	GEM	Prof Giovanni Vento	Rome, IT, EU
12	Careggi University Hospital	CRG	Prof Carlo Dani	Florence, IT, EU
13	Fondazione Monza	MBBM	Dr Camilla Rigotti	Milan, IT, EU
14	Filippo del Ponte Hospital	FDP	Dr Ilia Bresesti	Varese, IT, EU
15	Academic Teaching Hospital	ATH	Prof Burkhard Simma	Feldkirch, AUT, EU
16	Antoine Beclere Medical Center / South Paris University Hospitals	ABM	Prof Daniele DeLuca	Paris, FR, EU
17	Poznan University of Medical Sciences	POZ	Dr Tomasz Szczapa	Poznan, PL, EU
UK SITES				
18	James Cook University Hospital	JCU	Dr Prakash Loganathan	Middlesbrough, UK
19	Southmead Hospital	SMH	A/Prof Charles Roehr	Bristol, UK

20	Royal Hospital for Children Glasgow	RHCG	Dr Joyce O'Shea	Glasgow, Scotland
21	University Hospital Wishaw	UHW	Dr Karen McCall	Wishal, Scotland
22	University Hospitals of Leicester	LEI	Dr Joe Fawke	Leicester, UK
23	Royal Infirmary Edinburgh	EDIN	Dr David Quine	Edinburgh, Scotland
24	Birmingham Heartlands Hospital	UHB	Dr Harsha Gowda	Birmingham, UK
NORTH AMERICAN SITES				
25	Hospital of the University of Pennsylvania	HUP	A/Prof Elizabeth Foglia	Philadelphia, PA
26	University of Arkansas for Medical Sciences	UAMS	Prof Sherry Courtney	Little Rock, AK
27	Sharp Mary Birch Hospital for Women & Newborns	SMB	A/Prof Anup Katheria	San Diego, CA
28	Indiana University / Riley Hospital for Children	RIL	Dr Bobbi Byrne	Indianapolis, IN
29	Rady Children's at Rancho Springs Medical Centre/UCSD	RSMC	Dr Richard Song	San Diego, CA
30	Rady Children's at Scripps Memorial Hospital La Jolla/UCSD	SLJ	Dr Sandra Leibel	San Diego, CA

3.9 Participating Site Team

Each site Principal Investigator (PI) is responsible for the oversight of the research study locally, ensuring that Ethics Committee (EC) approval is obtained prior to study initiation, and that the trial is conducted in accordance with the protocol and all local regulatory requirements.

The PI will identify a POLAR Study Team comprising of the following core group of individuals who will be responsible for adhering to the study protocol and manual of procedures:

- Neonatologists
- Nurse Practitioners
- Research Nurses
- Respiratory Therapists
- Research Coordinators/Study Coordinators
- Other Clinical Care Team Members, as required

A Neonatologist will lead the clinical team which should include clinicians trained in how to perform the delivery room (DR) intervention (Static and Dynamic PEEP), clinical team assisting in the delivery room procedures and research team members who will collect study data, communicate with the DR and NICU team, and document trial events. The composition of the team may vary among sites.

The Research Coordinator (RC)/Member of the Clinical Care Team will be responsible for the coordination of study activities at the clinical site to ensure implementation of study procedures and data quality standards. The Research Coordinator/Member of the Clinical Care Team will work closely with the POLAR Trial Coordinator of the Data Coordinating Centre (DCCe) to facilitate study communications and information exchange.

4.0 Information Distribution

The POLAR DCCe will use a variety of tools to provide research team members with information and updates regarding the trial.

4.1 POLAR Trial Website

The POLAR Trial website contains both a public access landing page accessible to all users and the general public, as well as a private members portal containing information and documents pertaining to the study.

The public access landing page will allow parents and families and the public to access information and periodic updates about the trial.

The private members portal of the website will require a username and password in order to gain access. All study team members will be provided with username and password. (Note: A different username and password is needed for the limited group who will enter data into the POLAR REDCap database.) The portal will provide all members with one interface from which to access training videos, study updates, all trial-related documents, a link to the POLAR study databases (i.e., REDCap), as well as all study manuals and forms.

4.1.1 Accessing the POLAR Website

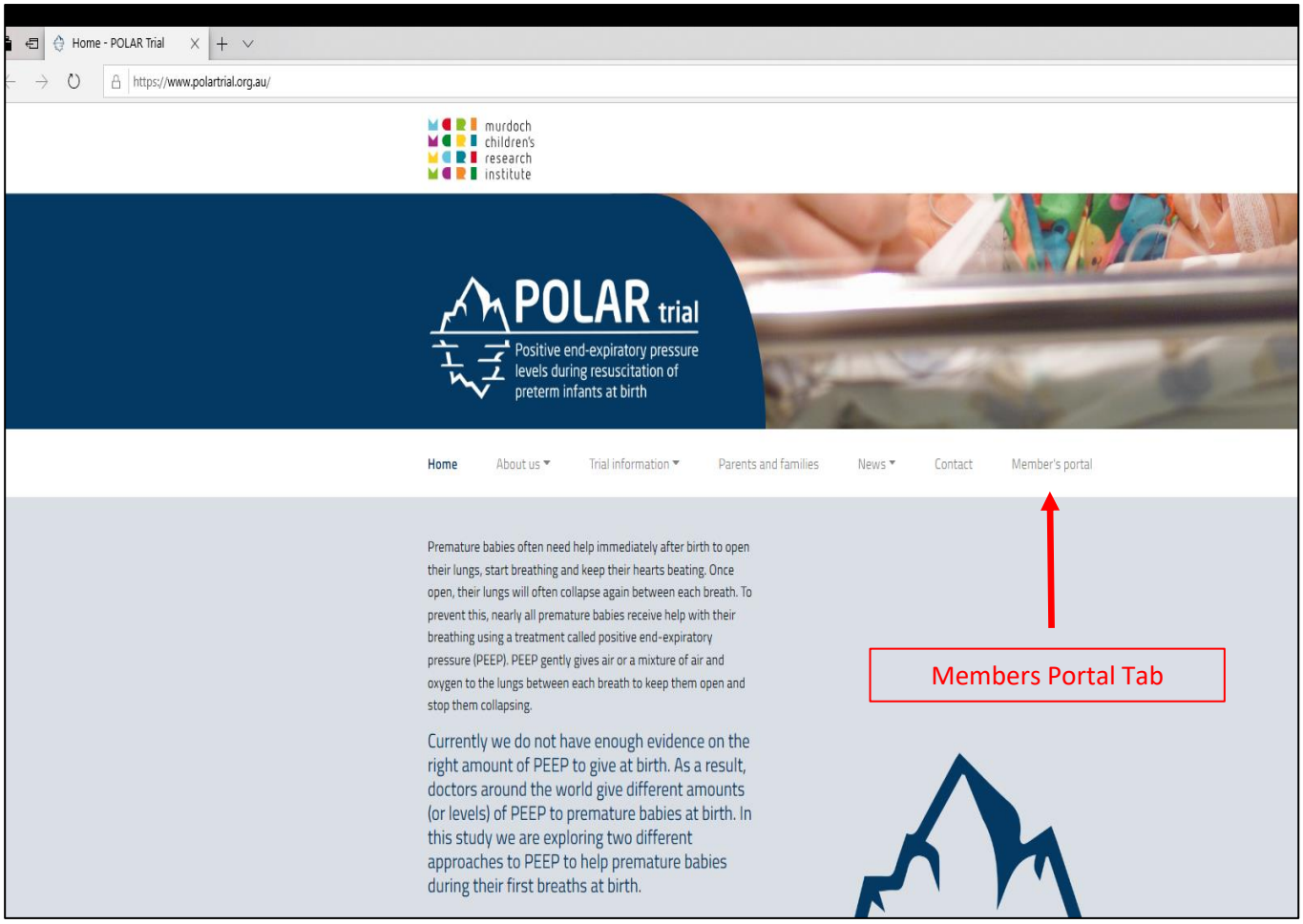
The POLAR website is located at www.POLARTrial.org.au

The landing page contains key facts regarding the trial and a quick link to a list of the participating centres involved in the study.

To gain access to the private members portal of the website, users must email the DCCe requesting access: POLAR@mcri.edu.au

Once you have been issued a username and password (via email) you will now be able to log into the private members portal of the website, which contains all the relevant study tools and documents. To log into the private portal, follow the steps as outlined below:

1. Navigate to the POLAR Trial website at www.POLARTrial.org.au
2. Click on the tab at the top right of the screen labelled 'Members Portal' and login with the username and password provided.



4.2 Email

DCCe personnel will also use email to communicate with participating sites and provide current information and trial updates to POLAR Trial collaborators and team members. DCC staff members are easily accessible by email and will reply to questions and requests for information as soon as possible.

Fortnightly trial email updates will also be circulated to all POLAR Trial collaborators and team members. If you would like to receive these email updates, please email the DCC at POLAR@mcri.edu.au to be added to the email distribution list.

4.3 Clinical Questions and Concerns

Urgent clinical questions and concerns, and questions regarding eligibility should be directed to the POLAR Trial Coordinating Centre (TCC) and Regional Leads (RLs) team leads accordingly.

To account for the differences in global time-zones, Regional Lead contact details have been provided in instances where an urgent response is required to a protocol or clinical question. Refer to the table below for a summary of contact details per region:

Role	Name	Email	Phone
POLAR Clinical Trial Manager c/o Trial Coordinating Centre	Ms Laura Galletta	POLAR@mcri.edu.au laura.galletta@mcri.edu.au	+61 3 9936 6448 +61 419 890 239
AUSTRALIA & NEW ZEALAND REGION			
Sponsor-Investigator / Coordinating Principal Investigator (CPI)	Prof David Tingay	david.tingay@rch.org.au POLAR@mcri.edu.au	+61 413 567 295
NORTH AMERICAN REGION			
Regional Lead – USA	A/Prof Elizabeth Foglia	foglia@email.chop.edu	+1 267-441-7144
EUROPEAN REGION			
Regional Lead – EU	Prof Anton van Kaam	a.h.vankaam@amsterdamumc.nl	+31-20-5664058
UNITED KINGDOM REGION			
Regional Lead - UK	Prof Charles Roehr	charles.roehr@npeu.ox.ac.uk	

5.0 Training and Documentation

5.1 Training on PEEP Delivery

At each site, the Site PI or his/her delegate will be responsible for delivery of local training. Specific training will be required for all clinicians who will be administering both the static and/or dynamic PEEP resuscitative interventions.

Training activities include the following:

- Reading the relevant section/s of the POLAR Protocol relating to your trial-related duties and/or functions, as applicable
- Review of the Site Initiation Presentation (slide set)
- Watching the POLAR training videos [see below Section 5.2]
- Review Section 8.0 of the POLAR Manual of Procedures (MOP) document: *Delivery Room Procedures*
- Attending local in-service session on infant resuscitation *(if applicable at your centre)*.

Upon successful completion of all the training activities listed above, clinicians will be required to complete the PEEP Training Attestation Checklist* to document their training. The Training Attestation form only needs to be completed by the clinicians who will be delivering the intervention.

**A copy of the PEEP Training Attestation Checklist is available on the POLAR Website, under the Members Portal.*

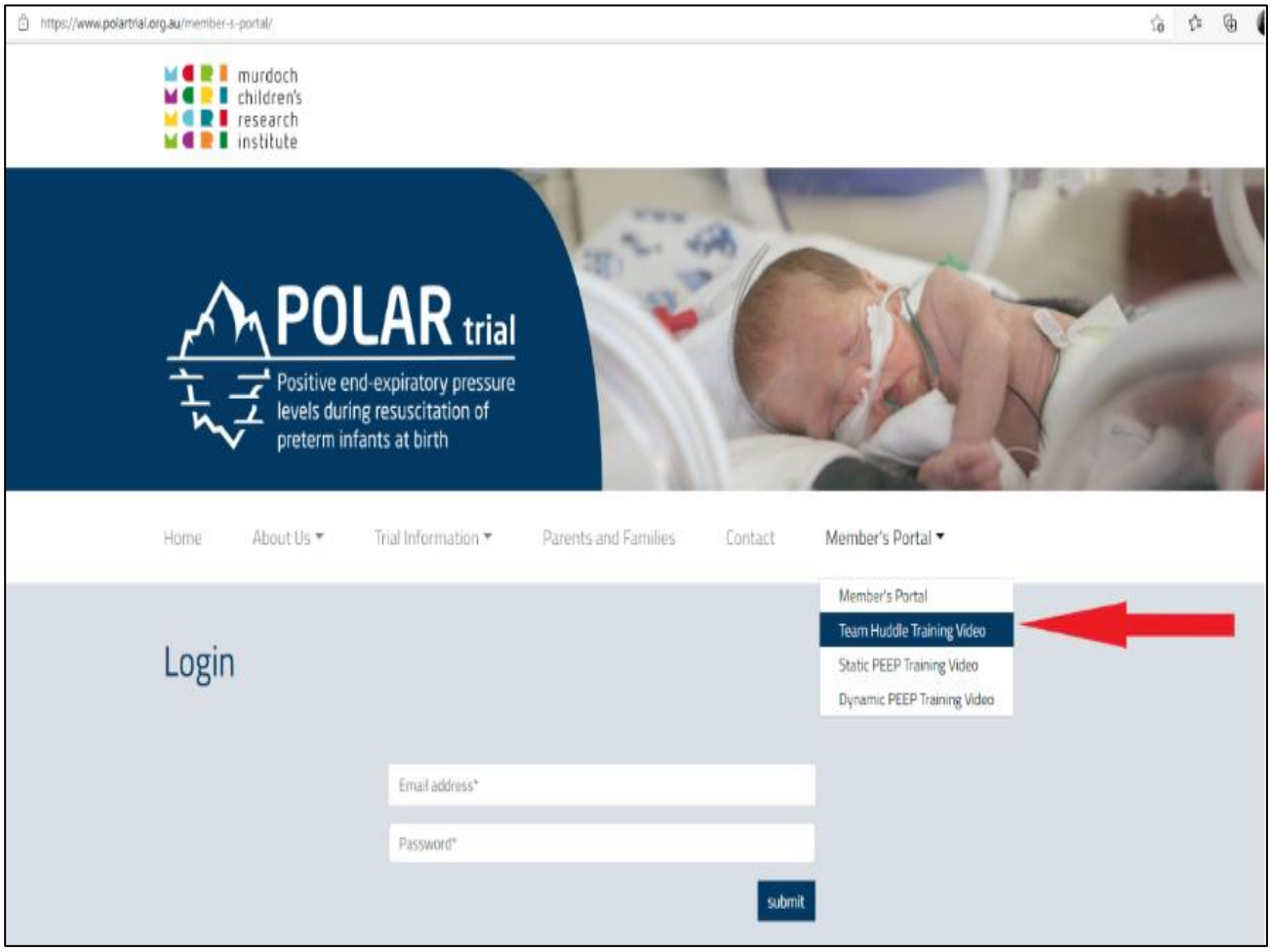
5.2 Accessing the POLAR Trial Training Videos

To facilitate training of clinicians, the team at the POLAR Trial Coordinating Centre has developed three (3) brief videos for use in training the delivery room team about the POLAR Trial PEEP delivery procedures. The training videos demonstrate the team huddle procedure and delivery of both the static and dynamic PEEP interventions and highlight the timing and coordination of events in implementing the intervention.

Aside from training the delivery room team during the trial planning and preparation stages, the videos can be viewed by any DR team before a POLAR eligible infant is born, to reinforce the procedure and timing. The videos demonstrate the team huddle and delivery of the intervention. They are not intended to show all possible scenarios.

Access to the training videos is via the POLAR Trial website:

1. Navigate to the POLAR Trial website at www.POLARTrial.org.au
2. Click on the 'Members Portal' tab on the top right-hand side of the menu bar
3. Please ensure you have your Member's Portal credentials handy to log into this area
4. Log into the Members Portal
5. Click on each video to view the training



Reach out to the POLAR Trial Coordinator (POLAR@mcri.edu.au) if you have any issues accessing the videos. Also, a handy hint to click on the "Arrows" in the far-right hand corner of each video to expand the view to full screen when watching the training videos.

5.3 Florence eBinders™ - Electronic Investigator Site File (eISF)

All participating sites will be provided with access to an electronic Investigator Site File (eISF) platform via the Florence eBinders™ platform to maintain and manage their essential documents for the trial.

Florence eBinders™ is a fully validated and 21 CRF Part 11, ICH-GCP, HIPAA and GDPR compliant cloud-based electronic Investigator Site File platform, which will enable remote monitoring by the Sponsor of all essential and trial-related documentation at the site level, to ensure overall compliance with ICH-GCP, the trial protocol and other regulatory requirements.

Florence eBinders acts in the exact same way as maintaining a paper ISF-binder, but rather than maintaining hard-copy documents, documents can be maintained electronically via this compliant platform.

5.3.1 Florence eBinders™ Training Requirements

Training must be completed prior to access being granted to your site folder. Full training is provided to all site investigators and site staff on the Florence eBinders™ platform by way of an online webinar.

The online training webinar consists of one training session targeted to site Research teams focussing on various functions the platform offers, such as executing e-signatures within the platform, uploading, redacting, and annotating documents, setting placeholders and expiry dates, and responding to assigned tasks. All site staff requiring access to Florence must complete this mandatory training, otherwise access will not be granted.

To enrol into the Florence eBinders™ training webinar, users must email the POLAR Trial Coordinator at: POLAR@mcri.edu.au

Additional training resources provided include the provision of a number of user guides and manuals, along with e-Signature Workflows and eISF Filing Guidance documents. These training resources are available on the POLAR Trial website.

5.3.1 Florence eBinders™ Homepage

The Florence eBinders™ homepage is located at: https://auth.uatv2.researchbinders.com/#/sign-in

5.4 Site-Specific PEEP Algorithm Authorisation

Due to regional differences in neonatal resuscitation program training and language, each participating centre can request to amend the Static PEEP and Dynamic PEEP algorithm templates 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.

All alterations to the Delivery Room algorithms must be approved **in advance** by the Trial Steering Committee (TSC) and included in any delivered site training. A set of editable static and dynamic PEEP Algorithms are available on the POLAR Website. They provide pre-approved alternative example algorithms which can be amended to suit local practices.

Please submit both **tracked and clean** copies of your site-specific algorithm/s to the Trial Coordinating Centre for approval by the POLAR TSC, **prior to your scheduled site initiation meeting,** as your approved site-specific algorithm/s will be used as training tools during your site initiation visit.

Site-Specific PEEP Algorithms are to be submitted via email to the POLAR Trial Coordinating Centre (TCC): POLAR@mcri.edu.au

Upon receipt, the algorithms will be reviewed by a representative of the TSC, and approval provided for use at your site.

5.5 Site Initiation Meetings: Training on Protocol & Data Management Procedures

The DCCe/TCC will hold a training webinar, via a Site Initiation Meeting, with each participating site and key research team members, prior to officially activating each site to enrolment and randomisation.

The 90-minute Site Initiation meeting will review key elements of the protocol, provide an overview of the trial's randomisation procedures and trial intervention, review of the manual of procedures (MOP) document and data collection and maintenance methods. The Site Initiation training will comprise of 3 key components: including but not limited to the following:

1. Part 1 – Clinical Component
    - Clinical Background and Hypothesis
    - Aims and Objectives
    - Study Design
    - Eligibility and Consent Procedures: Antenatal & Deferred
    - Study Intervention / PEEP Algorithms
    - Randomisation Procedure in the DR
    - Schedule of Activities
    - Safety Reporting: AEs / SAEs / URSAEs

2. Part 2 – Operations and Logistics Component
    - Site Staff Responsibilities
    - POLAR Website & eISF Maintenance
    - Key Trial Documents
    - Informed Consent & Screening Process
    - Randomisation Process / Randomisation Envelopes
    - Monitoring Compliance in the Delivery Room
    - Safety Reporting Requirements
    - Protocol Deviations and Serious Breaches
    - Monitoring; remote/central and on-site
    - Close-Out & Archiving

3. Part 3 – Database Overview and Training
    - Florence eBinders™ - eISF
    - Overview of the POLAR Electronic Data Collection System (eCRF)
    - CRF Completion Timeline / Guidelines
    - Data Entry Procedures

  - Screening Database
  - Main Study Database
- Source Documentation / SDV Requirements
- Recording AEs / SAEs
- Query Resolution Procedures

All the above training resources are available on the POLAR Trial website.

The POLAR Trial Manager will contact each site, once evidence of Ethics Committee approval has been provided, to arrange a mutually acceptable time to hold the Site Initiation Meeting

Sites will not be activated to enrolment and randomisation without undertaking this training webinar.

5.6 Summary of PEEP Training Requirements

Though the composition of the delivery room clinical team and research team varies at each site, some members of the delivery room clinical team may also be members of the site research team. Table 2 below provides a summary of study training required for clinical and research team members.

Table 2: Summary of Study Training Required for Clinical & Research Team Members

Role	Intends on delivering PEEP intervention in the DR?	PEEP Training Required & Completed Training Attestation Form	Is a Member of the Research Team?	Signs the POLAR Training Log	Signs the POLAR Signature & Delegation Log	Signs the Wet-Ink Signature Log^
Principal Investigator and/or Co-Investigators in charge of Research Team	YES	YES	YES	YES	YES	YES
Neonatologist/ Neonatal Fellow in charge of Delivery Room Team (Team Leader)	YES	YES	YES	YES	YES	NO
			NO	YES	YES	NO
Neonatologist/ Neonatal Fellow	YES	YES	YES	YES	YES	NO
	YES	YES	NO	NO	NO	NO
Other Delivery Room Clinicians such as: Respiratory Therapist; Nurse Practitioner; Nurse; Paediatric Resident; Physician Assistant	YES	YES	YES	YES	YES	NO
	NO*	NO	NO	NO	NO	NO
Neonatal Nurse assisting with delivery room care/or recording resuscitation information	NO*	NO	YES	YES	YES	NO
			NO	NO	NO	NO
Research Nurse / Clinical Research Coordinator	YES	YES	YES	YES	YES	YES
	NO	NO				

**Unless under direct supervision of a Neonatologist or Neonatal Fellow*
^Only if access is required to the Florence eBinders Platform, for the purpose of executing e-Signatures within the platform and maintenance of the electronic Investigator Site File (eISF).

5.7 Essential Documents & Approvals Required Prior to Site Initiation Meeting

Prior to conducting the Site Initiation Meeting at each individual participating site, copies of the following documents must be provided to the DCCe:

- Complete copy of your initial Ethics Committee application
- Ethics Committee/IRB/REB letter providing approval to conduct the study
- A copy of your Ethics Committee/IRB Membership List or Compliance Statement
- Regulatory Approval from your Competent Authority/Regulatory Authority: *if applicable*
- Research Governance Office Approval Letter (SSA): *Australian sites only!*
- Confirmation of Capacity & Capability (R&D Approval): *UK sites only!*
- Copies of your Ethics Committee approved site-specific Participant Informed Consent/Patient information document(s) – both Prospective (antenatal) and Retrospective (deferred) Consent forms (if applicable at your site): *on site letterhead*
- Copy of your Ethics Committee approved Privacy Notice: *UK and EU sites only!*
- Site Investigator Protocol Signature & Agreement page (located on Page 10 of protocol) signed by the Site Principal Investigator
- Principal Investigator's CV and GCP Certificate: *signed and dated*
- Sub-Principal Investigator's CV's and GCP Certificate's: *signed and dated*
- Clinical Research Coordinator's/Study Coordinator's CV's and GCP Certificate's: *signed and dated*
- Clinical Trial Research Agreement: *signed and dated*
- Training Attestation Form: *completed, signed, and dated by* ***all members*** *of the research team who will administer the PEEP intervention*
- Site-Specific PEEP Algorithms – static & dynamic: *tracked and clean copies [refer to Section 5.4 above]*
- Source Document Plan & Submission Checklist: *completed, signed, and dated [refer to Section 12.6 below]*

The POLAR Trial Manager will contact each participating site to formally request the above documentation, prior to each scheduled Site Initiation Meeting.

It is also expected that copies of each of the above documents are maintained and stored within your site-specific POLAR eISF eBinders™ folder, which are in turn available for remote monitoring purposes by the Sponsor.

5.8 Essential Documents Required Post Site Initiation Meeting

Post conducting the Site Initiation Meeting at each individual participating site, copies of the following documents must be provided to the DCCe:

- Training Attestation Form: *completed, all remaining outstanding forms not previously provided - signed and dated by* ***all members*** *of the research team who will administer the PEEP intervention*
- Signature & Delegation of Authority Log*, identifying the roles and responsibilities of all members research personnel involved in conducting the trial; initialled, signed and dated*
- Site Staff Training Log: *completed, signed, and dated by* ***all members*** *of the research team involved in conducting the trial; signed and dated*

- Wet-Ink Signature Log: *completed, signed, and dated by* ***all members*** *of the research team involved in conducting the trial and who require access to Florence eBinders; signed and dated* ***by hand in wet-ink***
- Site Initiation Attendance Log: *completed, signed, and dated by* ***all members*** *of the research team who attended the Site Initiation Meeting.*

It is also expected that copies of each of the above documents are maintained and stored within your site-specific POLAR eISF eBinders™ folder, which are in turn available for monitoring purposes (either remote or on-site monitoring) by the Sponsor.

6.0 Participant Enrolment Procedure

The participant enrolment procedure refers to the tasks that each site undertakes to initiate participant accrual, beginning with identifying potential participants, screening, and consenting, and randomising.

6.1 Identifying Potential Participants

A clinical care team member or research coordinator/study nurse 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 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 upon the clinical site's consent approach, these women may be asked to consent for the trial at the prenatal visit.

6.2 Screening of Potential Participants

Screening will occur prior to an infant's birth, whereby, all admissions of pregnant women with likely or threatened premature birth before 28 completed weeks' gestation will be screened daily to ensure that eligible participants can be enrolled.

Research team members will review the mother's medical history to determine eligibility based on the inclusion/exclusion criteria outlined within the protocol. The Research Team member will explain the study to the parents after determining eligibility. If it is practical to do so (or in centers only allowing prospective antenatal consent) they will then explain the study to eligible mothers/parents.

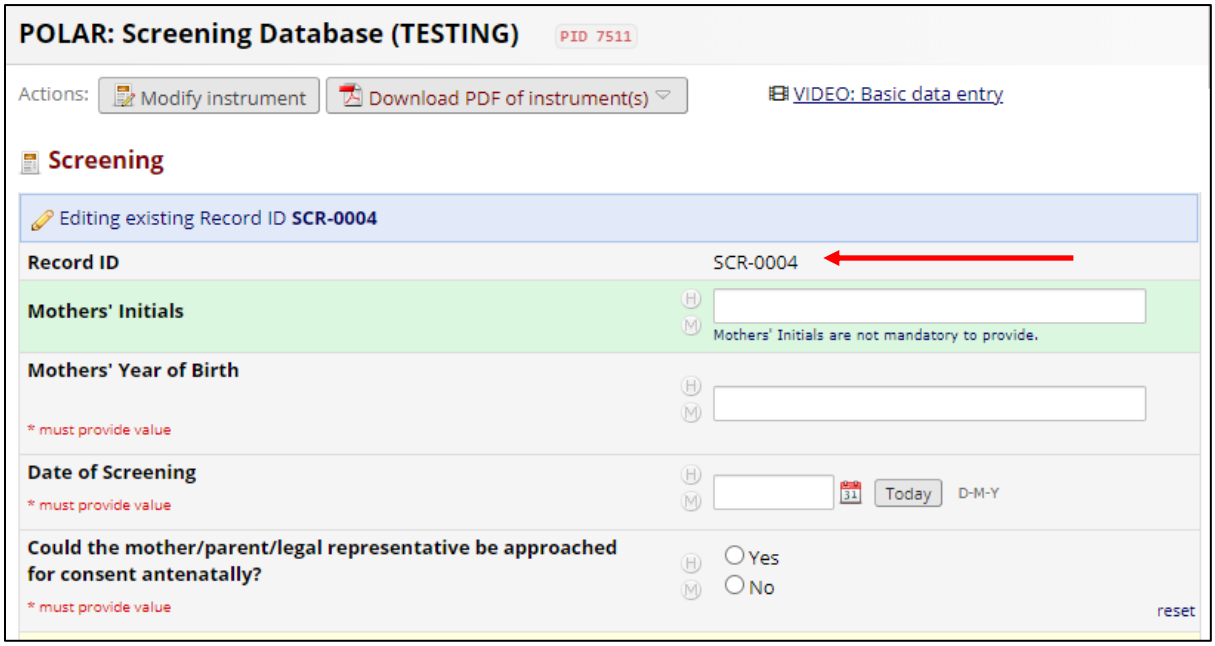
The research team at each site is required to maintain a screening database of all screened mothers-infants indicating who is eligible and who is not, and of eligible mothers who have consented to the study and who has refused study participation.

Screening logs will be maintained electronically (i.e., within REDCap) via the POLAR Screening Database, whereby all screened participants will be entered into REDCap.

6.2.1 Screening IDs and the POLAR Screening Database

Screening IDs will be automatically allocated by the POLAR Screening Database upon entry of the screened mother/infant into the REDCap Screening Database. The Screening ID is referred to as the "Record ID" within the POLAR Screening Database and will be a sequentially assigned digit beginning from 01, with the prefix of "SCR".

For example: SCR-0001, SCR-0002, SCR-0003 etc.



Note the Screening ID assigned to mothers/infants within the Screening Database is not carried over to the POLAR Main Study Database should infants be determined as eligible and proceed to randomisation. Infants are assigned a different unique Participant Identification Number (PID#) upon randomisation (Refer to Section 8.3.1 below for further information).

Please also refer to the POLAR CRF Completion Guidelines for further instruction on completing the POLAR Screening Database.

The initial step after screening is to obtain informed consent.

6.2.2 Screen Failures

Screen failures are defined as participants who consent to participate in the trial but are not subsequently randomised to 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 (mothers' year of birth only), screen failure details and eligibility criteria
- The above data will be captured in the POLAR Screening Database
- Refer to the POLAR eCRF Completion Guidelines for instructions on how to complete data entry on screened participants not randomised into the study.

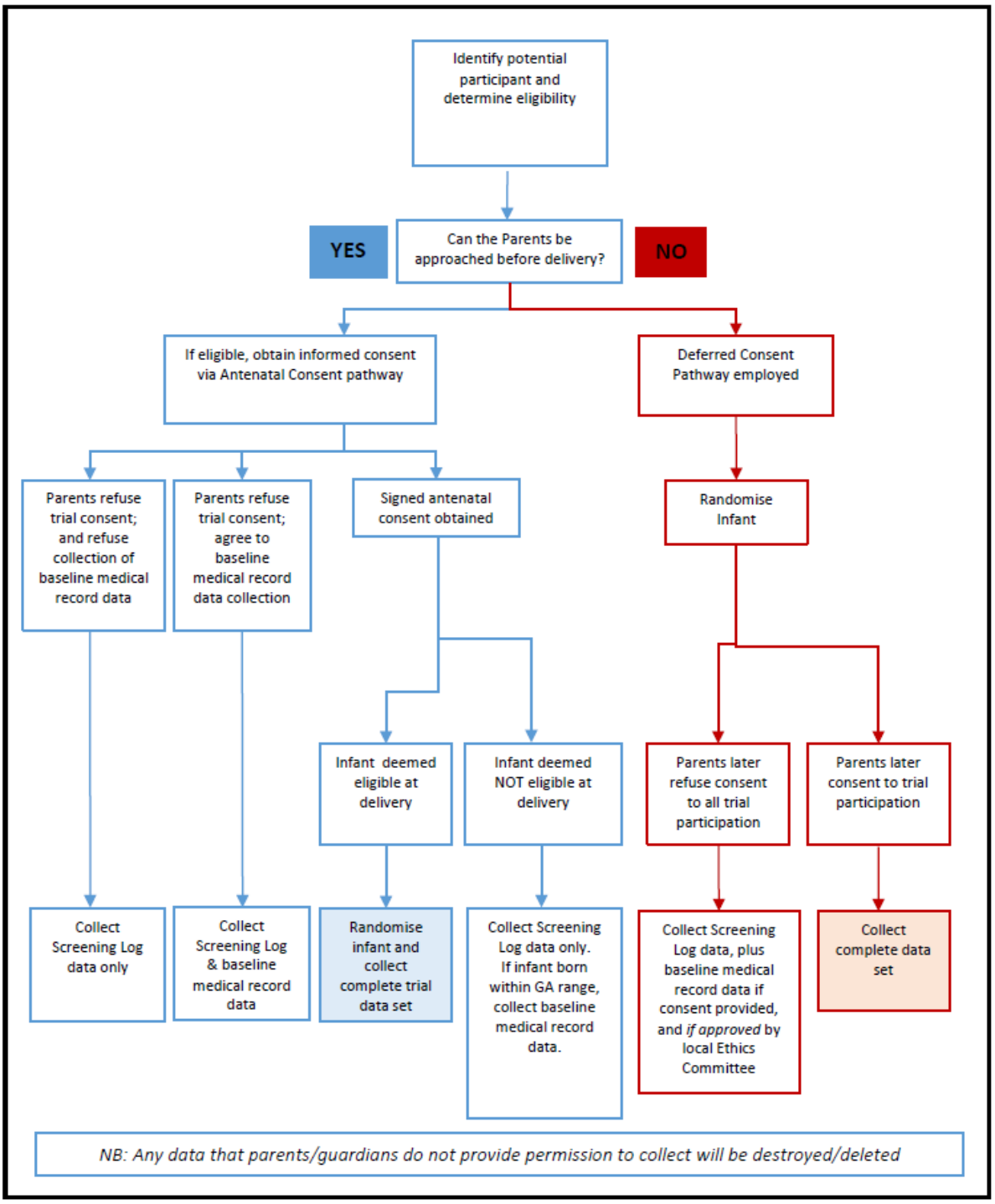
6.3 Informed Consent

Each participating site is responsible for ensuring that informed consent is obtained from each

participant according to the guidelines of its local Ethics Committee/IRB. The approaches used for obtaining informed consent, whether it be antenatal and/or deferred consent, as well as, the site-specific informed consent/patient information document used by the participating site, must be approved by the local Ethics Committee/IRB prior to initiating the study.

Informed consent will be obtained in one of two methods depending on local requirement, either antenatal consent approach or deferred consent approach (Refer to Figure 1 below). Antenatal (prospective) consent is the preferred method of consent for the POLAR Trial.

Figure 1. Flow Diagram of the Consent Process – Antenatal vs Deferred Consent



6.3 POLAR Parent Educational Video

Participating sites may wish to use the POLAR parent educational video/animation 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

- Should in no way be used in place of a full informed consent conversation which must be held with all participants
- Must be approved for use by each participating sites local Human Research Ethics Committee (HREC)/Institutional Review Board (IRB) prior to its use.

The educational video (currently in English, Italian, French, Spanish and Polish) can be accessed via the homepage of the POLAR website (www.POLARTrial.org.au) or via scanning the corresponding QR code for ease of accessibility:

English Video	Italian Video	French Video
Spanish Video	**Polish Video**	

Additional videos in other languages may be developed in due course. The MoP will be updated at this time, as well as additional QR codes which will point directly to the videos in other languages.

NOTE: The QR code is only to be used to access the parent education video and must not be used for publicly promoting or advertising the trial.

6.4 Prospective (Antenatal) Consent Approach

Parents will be approached for informed consent to enroll their infant into the study prior to

the infant's birth. Informed written parental consent will be obtained in the prenatal period from parents of potentially eligible infants presenting with threatened preterm birth within the inclusion gestations.

Infant(s) whose parents refuse to sign informed consent will also 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. This data will be recorded within the POLAR Screening Database and not within the POLAR Main Study Database. Refer to Section 6.0 of the CRF Completion Guidelines for further details regarding data entry requirements.

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 (Refer to Section 6.5).

6.4.1 Tracking Antenatal Consent Status

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 (i.e. decline antenatal consent) and are then discharged home, are NOT subsequently enrolled via the deferred consent pathway, should they present again at site precipitously.

6.5 Retrospective (Deferred) Consent Approach

At sites where the Ethics Committee/IRB permits waiver of prospective consent (or deferred consent) to be used, eligible participants will be randomized at birth, if prenatal consent was not possible, and resuscitation delivered as per allocated group.

The deferred consent approach is defined as consent that is obtained after delivery, randomisation, and resuscitation of the infant has occurred. In the POLAR Trial, the deferred consent approach can only be employed at sites, if this approach has been approved in advance by the local Ethics Committee/IRB, and it has been indicated as such, in the corresponding Ethics/IRB approval letter.

At sites that do not allow waiver of prospective consent and 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.

If a deferred consent is sought after resuscitation is completed in the DR, it is recommended that the parents are approached for consent to continue to collect study data, as soon as possible after delivery (but typically by Day 10), depending on the mother's health status.

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 is given for collection of such data; and
2. The Ethics Committee/IRB has approved this data collection.

The infant will not be included in the study.

6.5.1 Retention and Use of SAE Data from Participants who deny Consent

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

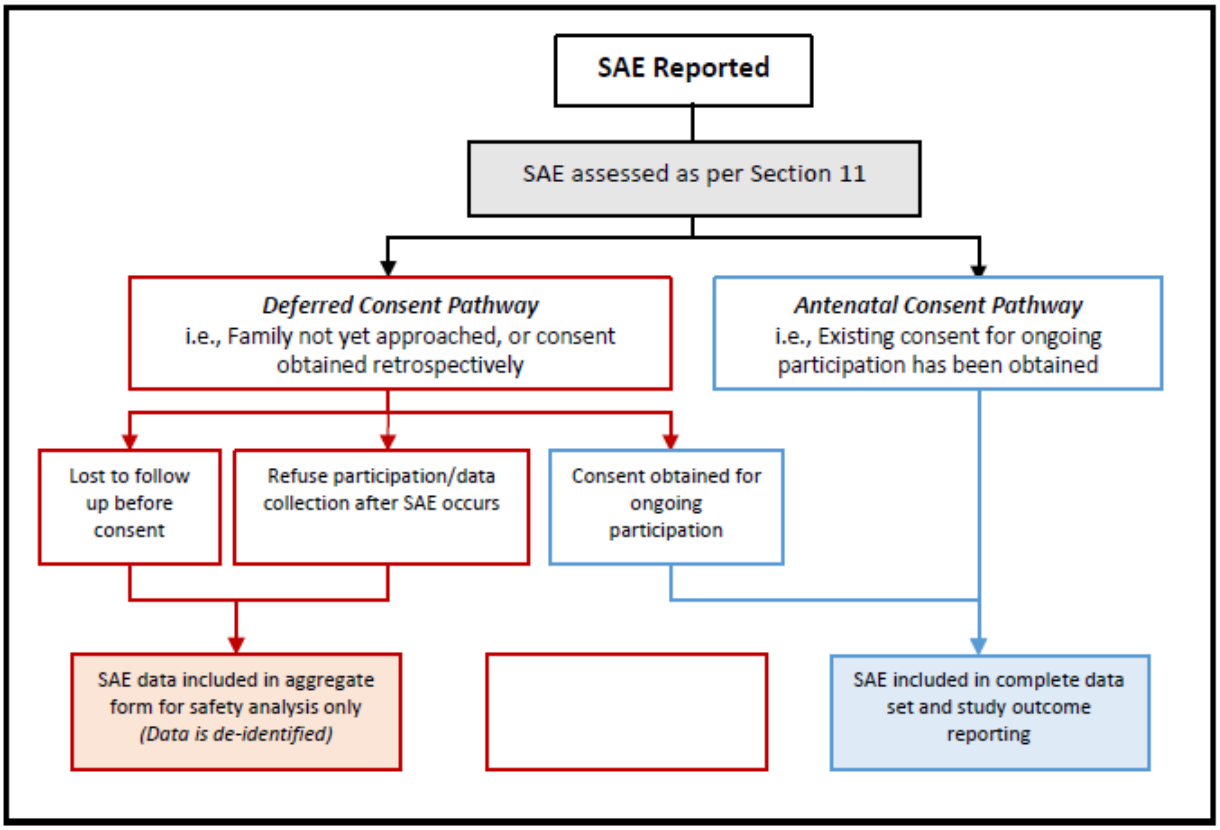
Should an SAE occur within the SAE reporting timeframe, and before deferred consent has been obtained (i.e. consent for continued participation in the trial), and consequently, consent is refused or cannot be obtained from the parents/guardians (for example family lost to follow up before approached for consent), the SAE must still be reported to the Sponsor in accordance with Section 11 of the protocol.

Data relevant to the SAE will be de-identified/pseudonymised and only included in total aggregate data assessed by the POLAR Medical Monitors (Refer to Figure 2 for the flow of SAE data). This de-identified data will also be made available to the DSMC, to assess if a suspected safety signal has occurred.

6.6 Documenting Informed Consent

Site Study Coordinators will maintain the original signed consent document in each participant's confidential research study file and provide a copy of the signed and dated informed consent to the participant. It is recommended that a second copy of all informed consent(s) should be made as a back-up and stored together in the study-confidential file. In addition, a signed/dated note should be written in each participant's research file documenting that informed consent was obtained. To ensure confidentiality, the Site Study Coordinator will not send copies of the informed consent form(s) signed by the participant to the DCCe or keep any copies of the informed consent form with the case report forms (CRFs).

Figure 2. Flowchart of SAE Data Collection by Consent Pathways



6.7 Health Insurance Portability and Accountability Act (HIPAA) Authorization

For participating sites based in the USA, participants are required to sign a Health Insurance Portability and Accountability Act (HIPAA) Authorization, in addition to the Informed Consent Form. Non-US based sites have a parallel arrangement. The HIPAA Authorization may or may not be incorporated into the text of the Informed Consent document, depending on the policy of the individual participating site. If the HIPAA language is incorporated into the Informed Consent document, the regulation mandates that it be submitted to the Ethics Committee/IRB for prior approval. This form describes both the kinds of health information collected in this study, and all the disclosures of health information that will be made. The form must also list parties to whom disclosures of personal health information will be made.

7.0 Eligibility & Enrolment

7.1 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.

7.1.1 Inclusion Criteria

Each infant must meet all the following inclusion 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 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).

7.1.2 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.

7.2 Participant Withdrawal of Consent

Parents are free to withdraw their infant from the study at any time. 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:

- 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.
- Decision to withdraw consent from trial is requested by the participants parents/guardians
- Site Principal Investigator determines it is in the best interest of the participant.

When the Research Team becomes aware of a study withdrawal, the 'Study Withdrawal' CRF within the POLAR REDCap main study database must be completed. Refer to Section 8.0 of the POLAR CRF Completion Guidelines for further details.

7.3 Handling of Withdrawals & Losses to Follow-Up

The trial will retain existing data already collected, as the research is being legally processed as a task in the public interest.

When a parent/guardian withdraws an infant from the study, the reason and/or type of withdrawal must be recorded on the 'Study Withdrawal' CRF within the study database.

Refer to Section 8.0 of the POLAR CRF Completion Guidelines for further details on how to complete the "Study Withdrawal" CRF.

7.4 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 should the following situations occur:

- The infant is subsequently identified as having an exclusion criterion (Refer to Section 7.1.2 above), or
- The infant was identified as still born post randomisation.

7.5 Site Participant Randomisation Log

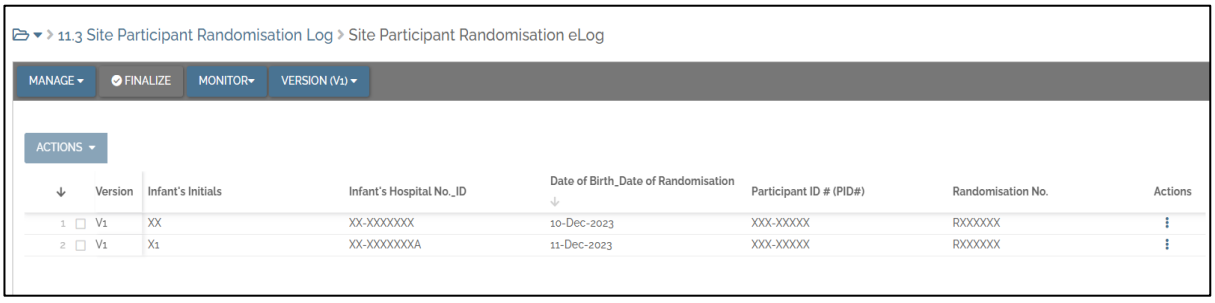
Each site is required to maintain a log of all infants who have been randomised into the trial. To facilitate this, the TCC provide participating trial sites with the following resources:

1. Paper based Site Participant Randomisation Log (available via the POLAR Trial website), or
2. Site Participant Randomisation Florence eLog

Site Participant Randomisation Logs must be maintained and kept up to date and filed in Folder 11.3: Site Participant Randomisation Log of your eISF in Florence eBinders.

The eLog can be used in place of the paper (word version) of the POLAR Site Randomisation Log and saves sites having to maintain a paper version of the Randomisation Log, update the paper log with enrolment/randomisation details, and then re-upload current versions into Florence eBinders each time a update is made.

Essentially, the Florence Site Participant Randomisation eLog allows users to add data directly into Florence eBinders, without the need of having to maintain a paper log and constantly download and re-upload versions into the platform – refer to example snapshot below:



8.0 Delivery Room (DR) Procedures

Immediately prior to birth of the infant in the Delivery Room (DR), determination of the infant's eligibility for the trial will be made. If deemed eligible, the infant will be randomly assigned to receive either static or dynamic positive end expiratory pressure (PEEP).

8.1 Delivery Room Resuscitation Team

A Neonatologist or delegate will lead the resuscitation team, which comprises of medical, nursing, and allied staff who will perform the DR intervention and all procedures. Some members of the clinical team may also be members of the research team.

The POLAR Trial is designed to allow randomisation and protocol intervention by the usual DR resuscitation team at a Site. At each DR resuscitation there will need to be a nominated delegate who will primarily collect trial-related data relevant to the protocol, communicate with the DR and NICU teams, and document trial events (e.g., a 'scribe'). Ideally this should be a member of the POLAR Trial Research Team. However, it is acknowledged that it is not always possible to have a member of the POLAR Research Team present at each delivery and that the exact composition of the delivery room team may vary among the participating sites. Sites must establish a process of communication and feedback of information to members of the POLAR Research Team, should they not be present at a delivery.

Table 3 below depicts and describes the composition and role designation for members of an example Delivery Room resuscitation team. This may serve as a potential model; however, the central POLAR Team acknowledges that this may vary at each participating site. The recommended minimum members of the resuscitation team in four (4).

Whilst team compositions are likely to vary across sites, the Site PI and the team leader at an individual resuscitation should consider which members of the available clinical team are responsible for performing these required duties and assign them accordingly at each delivery.

8.2 Team Huddle

If time allows, it is strongly suggested that the DR resuscitation clinical Team Leader, conducts a brief huddle of the team prior to the delivery of each infant (i.e., a 'Just-in-Time Training session). The purpose of a Team Huddle is to discuss the anticipated clinical interventions needed once the infant is born, assign roles to the clinical team and ensure that all staff are aware of roles, responsibilities, and actions. The Team Huddle is the ideal opportunity for the Team to randomise an infant to the POLAR Trial and integrate the allocated protocol into the planning process.

This session should review all required tasks and assignments and appropriately allocate responsibilities to each participating team member involved in the delivery room; specifically:

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

5. Perform the randomisation by selecting the next envelope in sequence within the correct GA stratum, including opening of the envelope, announcement to all members of the clinical team present and affirmation, and affirmation of the randomisation group assigned (once completed) by all team members
6. Review initial steps and timing for assessments of the allocated static PEEP (control) or dynamic PEEP (intervention) algorithm, including placing a laminated version of the allocated algorithm next to the T-piece PEEP resuscitator
7. Address all questions and concerns by members of the DR team
8. If time permits, briefly review the allocated intervention training video
9. A POLAR training video demonstrating the team huddle and the dynamic PEEP intervention algorithm is available at: www.POLARTrial.org.au
10. Access to the training videos is via the "Members Portal" tab at the top left of the homepage
11. Use your Username and Password to access the training videos via the POLAR website.

In some instances, i.e., emergency situations, the team huddle may only be very brief or non-existent. This should not preclude the enrolment of infants if there is adequate time before the delivery for the team to randomise the infant, open the next sequential envelope and prepare and select the allocated algorithm and equipment.

Table 3: Table Depicting the DR Team Composition

ROLE	ASSIGNED TO	DUTIES / RESPONSIBILITIES
Team Leader	Neonatologist or Fellow	▪ Leads Pre-Resuscitation Team Huddle ▪ Makes final determination of study eligibility and directs Research Team to open the randomisation envelope ▪ Ultimately responsible for ensuring adherence to assigned study intervention algorithm *(static or dynamic)* ▪ May not be involved with hands-on care ▪ Allocates POLAR Study Coach Role if no coach is available
POLAR Study Coach (*if available)*	Neonatal Nurse Practitioner, Fellow, or Nurse	▪ Assists Team Leader in ensuring adherence to intervention algorithm ▪ Uses stopwatch to ensure appropriate time intervals are used, counts down these intervals aloud for the team ▪ Anticipates and announces next step of algorithm in advance

Airway Provider	Neonatologist, Fellow or Nurse Practitioner	▪ Clears airway and manages the facemask/nasal prong ▪ Maintains and monitors mask seal *(if appropriate)* ▪ Assesses for visible spontaneous breathing pattern ▪ Adjusts PEEP level on Neopuff ▪ If necessary, occludes Neopuff to deliver the PIP ▪ If necessary, performs intubation
Additional Medical Provider	Fellow, Resident or Neonatal Nurse Practitioner	▪ Performs clinical HR assessment and assessment of breathing pattern ▪ If necessary, supports Airway Provider with mask/airway support, adjusting Neopuff settings, intubation to facilitate appropriate resuscitation delivery ▪ May perform other duties, such as achieving IV access, as necessary
Nurse 1 or Respiratory Therapist	Respiratory Therapist, Neonatal Nurse Practitioner or Neonatal Nurse	▪ Opens randomisation envelope and announces allocation ▪ Applies pulse oximetry probe and ensures signal stability ▪ Stimulates infant and applies plastic barrier/wrap for thermoregulation ▪ Adjusts FiO_2 ▪ Assists Airway Provider and Team Leader as directed ▪ May perform the roles of 'Additional Medical Provider' if appropriate ▪ Prepares +/- delivers medication ▪ Assists with clinical assessment of HR, breathing pattern, temperature measurement and control
Nurse 2 or Respiratory Therapist	Respiratory Therapist, Neonatal Nurse Practitioner or Neonatal Nurse	▪ As per Nurse 1 role
Scribe/ Data Recorder	Neonatal Nurse allocated to resuscitation scribe role	▪ Not involved in hands-on care ▪ Real time recording of time of delivery/birth, HR, respiratory effort: *may need to prompt team for these assessments* ▪ Prompts Team of algorithm steps ▪ Record all study interventions and infant's response to interventions ▪ Thereafter records resuscitation per protocol / DR paper CRF

NOTES:

1. A single provider may perform more than one role depending on the staffing and site model of care. The recommended minimum number of attendees is four (4).

2. The providers listed in each Assigned Role are not mandated in the POLAR protocol and alternative providers/craft groups can be used as per local practice.
3. The Trial Manager and PI's will finalise the DR Team Composition with each Site Coordinator during Site Initiation and Training.

8.3 Randomisation Process

An infant is randomised into the POLAR Trial when he/she has been determined as eligible, meeting all the inclusion criteria and none of the exclusion criteria and either informed prospective consent obtained or using an IRB approved deferred / retrospective consenting process. In the event of multiple births, infants will be randomised independently.

The following steps should be followed:

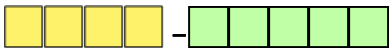
1. The randomisation process will occur in the Delivery Room (DR) ideally before the infant is born and with sufficient time to allow a Team Huddle
2. Randomisation can occur in emergent deliveries without the opportunity to perform a Team Huddle, as long as, randomisation occurs prior to the delivery of any PEEP
3. Randomisation envelopes must be kept in close proximity to the DR with adequate signage
4. The resuscitation team leader/neonatologist confirms the infant's estimated GA
5. 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)
6. In the event of multiple births, select the next envelope in sequence and assign an envelope to each infant independently according to birth order
7. The randomisation envelope is opened
8. The team member should loudly and clearly announce the randomisation group allocated
9. All team members acknowledge the randomisation group (closed loop communication), identify, and confirm correct laminated trial algorithm to be used
10. Review initial steps and timing for assessment(s) for the allocated static PEEP (control group) or dynamic PEEP (intervention group) algorithm, including placing a laminated version of the allocated algorithm next to the T-piece PEEP resuscitator
12. Address all questions and concerns by members of the DR team.

Once an infant is randomised, the Research Coordinator/Study Team/Member of the Clinical Care Team must enter the participant into the POLAR REDCap electronic data capture (EDC) platform, within 24-48 hours of birth, irrespective of whether deferred consent has been employed. The randomisation number assigned, randomisation date, allocation will need to be entered at this time.

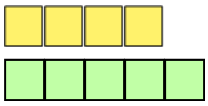
8.3.1 Participant Identification Numbers (PID#)

Unique Participant Identification Numbers (PID#) are automatically allocated by the POLAR Main Study Database upon entry of randomised infants into the REDCap database. It is therefore essential that the Research Coordinator/Study Team/Member of the Clinical Care Team enter the participant into the database within **24-48 hours of birth**, irrespective of whether deferred consent has been employed, so to ensure a PID# is assigned to randomised infants and that the Data Coordinating Centre (DCCe) is aware that the randomisation has occurred.

A unique PID# will be allocated to each randomised participant in the following format (this will be a strict sequential number):



Where:



where Site ID (i.e., RWH, KEMH, HUP)*

where Sequential Number, **00001 to 99999**

For example:

Participant ID Numbers for RWH:	RWH-0001 to RWH-99999
Participant ID Numbers for KEMH:	KEMH-0001 to KEMH-99999
Participant ID Numbers for HUP:	HUP-0001 to HUP-99999

*Note: The Site ID can either be assigned as 3 or 4 letters e.g., RWH, KEMH, HUP etc.

Refer to Table 1 above for a listing of all participating sites and their corresponding Site ID.

Please refer to the POLAR CRF Completion Guidelines for further details regarding how to enter randomised participants into the database.

8.4 Randomisation Envelopes

Sealed opaque randomisation envelopes will be provided by the Data Coordinating Centre (DCCe) to each participating site just prior to site activation. Envelopes will be initially provided to each participating site in batches of 15 envelopes for each stratum (i.e., 30 envelopes in total).

Randomisation envelopes are colour-coded by stratum to reflect the different gestational age (GA) groups:

- 23-25 weeks GA envelopes are RED
- 26-28 weeks GA envelopes are BLUE

Each envelope will display the following identifiers and will be sequentially assigned to infants in that stratum:

- Site ID i.e., RWH, KEMH, HUP, AMC etc.
- Gestational Age Group
- A sequential 3-digit number i.e., 001, 002, 003, 004 etc.
- The Randomisation Number i.e., Rxxxxxx

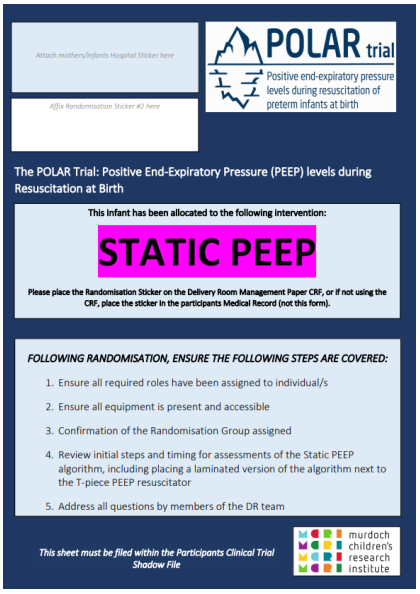
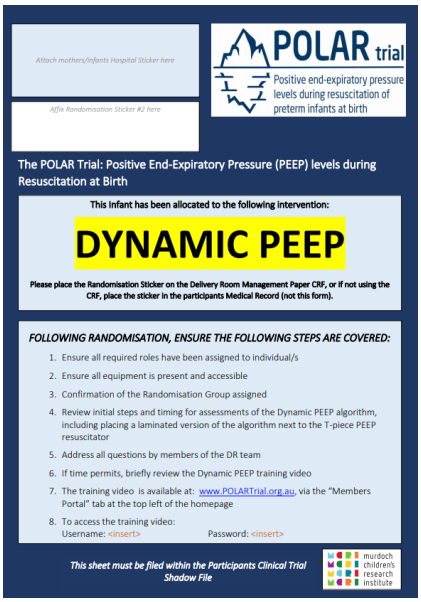
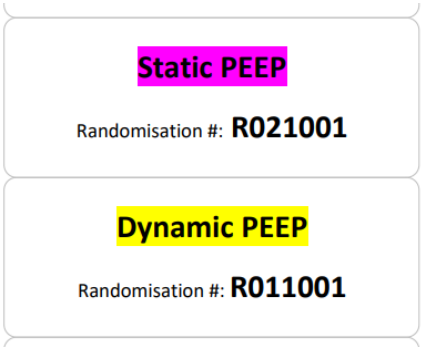
The envelopes must be kept in close proximity to the Delivery Rooms at participating centres, at an appropriate location to be documented during site start-up procedures as well as on the "Randomisation Envelopes – Acknowledgement of Receipt" form. The envelopes should be easily accessible and ready to open for allocation once the Team Lead has verified eligibility.

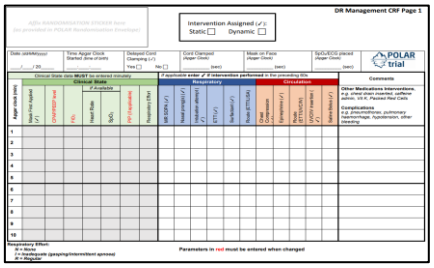
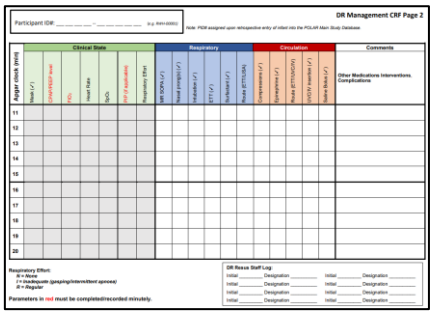
Refer to Figure 3 below of an actual image of the outside of the Randomisation Envelopes for the study. Note: these are sample envelopes generated for training purposes only.

Figure 3: Image of the Outside of the POLAR Randomisation Envelopes

8.4.1 Contents of each Randomisation Envelope

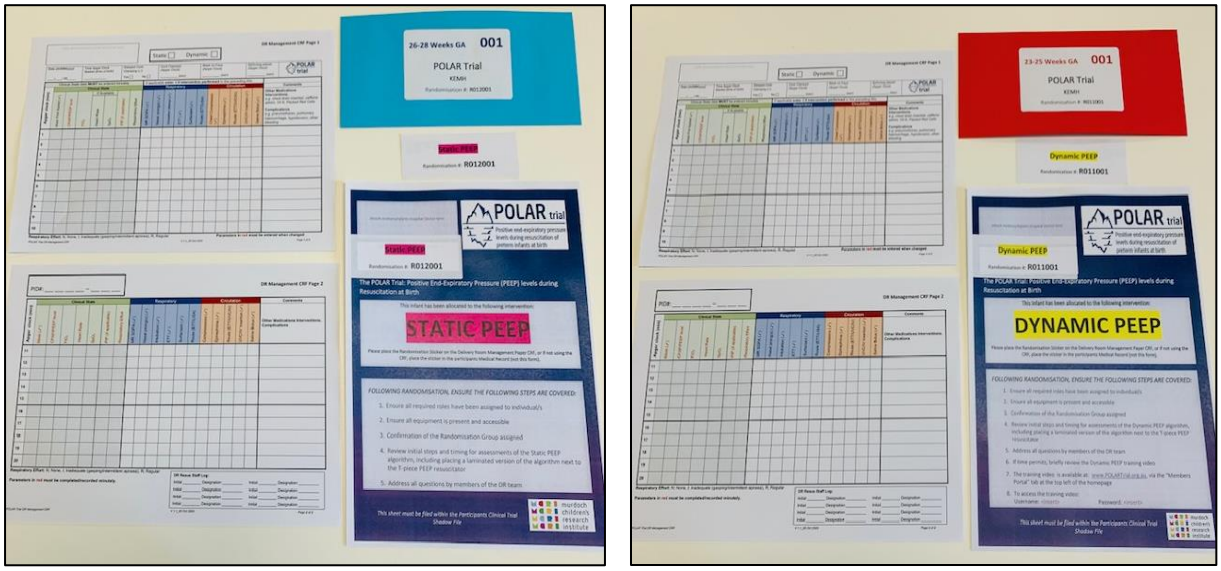
Each Randomisation Envelope will contain the following items:

1.	A4 Randomisation Sheet	 	▪ The A4 Randomisation Sheet outlines brief instructions to be followed post randomisation to ensure the correct management of the infant. ▪ Site staff are required to attach the infant's Hospital Sticker to the top left-hand corner of this A4 sheet. ▪ This sheet must then be filed within the participants' clinical trial shadow folder at the Site.
2.	1 x Randomisation Sticker		▪ The randomisation sticker displays the randomisation number and the assigned allocation. ▪ Site staff must append this sticker to the Delivery Room Management paper CRF (if using this CRF). Otherwise append this sticker to the infants' medical record.

3.	Delivery Room Management Paper CRF	 	▪ The Delivery Room Management CRF has been designed as a paper CRF, to allow real-time recording of key clinical and physiological data points used in the NRP algorithm, by the Delivery Room Team 'scribe'. ▪ The randomisation sticker will be attached on the Delivery Room Paper CRF by the site stuff. ▪ The Delivery Room Management paper CRF will be entered into the trial database at a later more convenient time by the Research Team. ▪ This Delivery Room Management paper CRF must then be filed within the participants' clinical trial shadow folder at the Site. ***Note: Sites also have the option of using their own local Resus Form/Code Sheet within the DR to capture this data. If Sites intend on using their own local form, a copy of the form must be provided to the POLAR Trial Coordinating Centre prior to site activation for approval by the TSC.***

Refer to Figure 4 below of an actual image of the contents of sample Randomisation Envelopes for the study. Note: these are sample envelopes generated for training purposes only.

Figure 4: Image of the contents of POLAR Randomisation Envelopes



8.4.2 Acknowledging Receipt of Randomisation Envelopes

Upon receipt of the Randomisation Envelopes from the DCCe, participating sites must confirm receipt of the envelopes by returning the "Randomisation Envelopes – Acknowledgement of Receipt Form" which will have accompanied the envelopes:

- Completed and signed forms must be emailed to the POLAR Trial Manager at the Data Coordinating Centre: POLAR@mcri.edu.au
- The original copy of the form must be filed within your site-specific POLAR eISF eBinders™ folder.

**A copy of the Randomisation Envelopes – Acknowledgement of Receipt Form is available on the POLAR Website.*

8.4.3 Re-Ordering of Randomisation Envelopes

Once ten (10) randomisations have occurred in either stratum, please email the POLAR Trial Manager (POLAR@mcri.edu.au) so that the next batch of randomisation envelopes can be prepared and be mailed to your site. Subsequent re-ordering of randomisation envelopes must occur when a minimum of five (5) envelopes are remaining at site within either stratum.

Note: The preparation of randomisation envelopes is not an automated procedure, and the DDCe will be relying on your email notification in order to commence preparing your center's next batch of envelopes.

8.4.4 Storing of Opened Randomisation Envelopes

For quality assurance and monitoring purposes, it is important that opened randomisation envelopes are saved and filed within the infant's clinical trial participants

shadow file. This must occur in a timely manner after the infant leaves the delivery room. Opened envelopes will be QA'd during on-site monitoring visits by the unblinded study monitor.

8.4.5 Destruction of Unused/Un-Opened Randomisation Envelopes at Randomisation Closure

All unopened envelopes remaining at participating study sites at closure of randomisation must be destroyed locally. Confirmation of the destruction of unused Randomisation Envelopes is documented by the completion of the "Acknowledgement of Randomisation Closure & Destruction of Envelopes" form, noting on this form the sequential and randomisation number of each individual envelope destroyed at site.

Completed and signed forms must be returned to the DCCe for reconciliation purposes by the unblinded Independent Statistician at the end of the study. You will be prompted by the POLAR Trial Manager when randomisation closure occurs and when you may proceed to destroy any unused envelopes.

**A copy of the Acknowledgment of Randomisation Closure and Destruction of Envelopes Form is available on the POLAR Website.*

8.5 Important Randomisation Guidelines

- The envelope with the lowest available sequential number for a given stratum should be used
- Randomisation envelopes must only be opened at or immediately before an infant's birth or during the Team Huddle process prior. Randomisation envelopes must not be opened well in advance of anticipation of an infant's birth.
- If a randomisation envelope is opened and is not used, that randomisation number should not be used for another eligible infant, and it should be reported to the DCCe as soon as possible, as this will alter the randomisation scheme. Such envelopes should also be saved and reported to the DCCe.
- In the event of multiple births, infants will be randomised independently.
- If a randomisation envelope is opened in error, a Non-Compliance Report Form (i.e., Major Protocol Deviation) must be completed within 24 hours of the event and emailed to the DCCe/POLAR Trial Manager explaining the situation.

**A copy of Non-Compliance Report Form (Protocol Deviation Form) is available on the POLAR Website.*

8.6 When is a Randomisation Envelope Not Opened?

A randomisation envelope is not opened when:

- It is determined at birth that an infant is not eligible for the trial
- Parents/Guardian's refuse to provide antenatal/prospective consent for the study (note: it is appropriate to open a randomisation envelope in situations where deferred consent is employed).

8.7 Breaking of the Study Blind

Breaking of the assigned intervention/study blind is not applicable as the intervention allocation will be known to the clinical team within the DR following randomisation, as well as the Research Coordinator/Study Team/Member of the Clinical Care Team at site.

Note: a reminder that the Trial Coordinating Centre (TCC) based at the Melbourne Children's Trial Centre (MCTC) is blinded to the allocated study intervention, until unblinding occurs at the end of recruitment.

9.0 Study Visits and Procedures

9.1 Study Timeline and Schedule of Assessments

Table 4 details the study timeline and schedule of assessments.

Table 5 details the studies Table of Procedures.

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).

Data related to protocol compliance and pre-specified primary and secondary outcomes will be collected to capture the DR care and then NICU management at the following time points:

- Baseline/Delivery Room
- First 24 hours of life (after discharge from DR)
- First 72 hours of life
- First 7 days of life
- First 10 days of life
- At 36 weeks PMA
- As appropriate throughout the entire hospital stay in order to capture primary and secondary outcome data
- A follow-up visit will occur at 24-months (+/- 2 months) to assess 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.

Table 4: Study Timeline and Schedule of Assessments

TIMEPOINT	SCHEDULE	ASSESSMENTS	
$t_{pre-delivery}$	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)*
$t_{pre-delivery}$	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.

Table 5: 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 (deferred)	Informed consent will occur through a prospective or deferred method, dependent on site HREC/IRB approval.
Randomisation	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).
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 of the protocol.
Dynamic	First 20 min from birth	Delivery of a positive end-expiratory pressure

Intervention: PEEP 8-12 cmH_2O range	only	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 of the protocol, 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 (As per Table 7.1 of the protocol) 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 (refer to Table 7.1 of the protocol), 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 of the protocol.
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 (as per section 11.0 of the protocol).
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. '

9.2 Forms Completed at each Assessment

Table 6 details the schedule of assessments and the corresponding form/CRF completed at each assessment.

Table 6: Form/CRF Completed at Each Assessment

TIMEPOINT	SCHEDULE	FORM/CRF NAME	DATABASE
$t_{pre\text{-}delivery}$	Screening Information	Screening	POLAR Screening Database
t_0 (Baseline)	Delivery Room Management & Outcomes *(i.e., Parents who refuse trial consent but agree to medical record data & the infant was born <29 weeks GA*)	Delivery Room	POLAR Screening Database
$t_{pre\text{-}delivery}$ (Baseline)	Consent History & Ethnicity	Participant Information and Consent	POLAR Main Study Database
t_0 (Baseline)	Eligibility Confirmation	Eligibility and Randomisation	POLAR Main Study Database
t_0 (Baseline)	Allocated Randomisation Number	Eligibility and Randomisation	POLAR Main Study Database
t_0 (Baseline)	Demographic Information – Mother & Infant	Demographic Details	POLAR Main Study Database
t_0 (Baseline)	Details of the Intervention applied in the DR & physiological parameters	Delivery Room Protocol Intervention	POLAR Main Study Database
t_0 (Baseline)	Delivery Room Outcomes	Delivery Room Outcomes	POLAR Main Study Database
t_0 (Baseline)	Compliance Review - w*ithin 5 days of birth*	Intervention Compliance Self-Assessment	POLAR Main Study Database
t_1 (24 hours)	NICU - Day 1 respiratory status assessment	Respiratory Care – First 24 Hours	POLAR Main Study Database
t_{72} (72 hours)	NICU - Day 3 respiratory status assessment	Respiratory Care – First 72 Hours	POLAR Main Study Database
t_7 (7 days)	NICU – Day 7 respiratory status assessment	Respiratory Care – Day 7	POLAR Main Study Database
t_{10}	NICU - Day 10 respiratory status assessment	NICU Day 10 Status	POLAR Main Study Database
t_{prn}	Intervention Failure within the first 72 hours	Failure of non-invasive ventilation in first 72 Hours	POLAR Main Study Database
t_{prn}	AE/SAE – *as occurs*	Adverse Events	POLAR Main Study Database
t_{prn}	Protocol Deviations – *as occurs*	Protocol Deviation	POLAR Main Study Database

t_{prn}	NICU – Details of NICU stay and final outcomes status assessments	- Final NICU Disposition - Final Respiratory Outcomes - Final Neurological Outcomes - Final Retinopathy of Prematurity Status - Final Other Outcomes	POLAR Main Study Database
$t_{36\ PMA}$	Assessment of BPD Status at 36-weeks PMA *(Primary Endpoint Assessment)*	36 Week CGA BPD Assessment	POLAR Main Study Database
$t_{24\ months\ corrected}$	24-months PMA assessment / Formal Neurodevelopmental assessment *(Tertiary Endpoint Assessments)*	- Follow-Up Status - Two-Year Follow UP Form - PARCA-R (if applicable)	POLAR Main Study Database
t_{prn}	Documentation of Withdrawal of Consent	Study Withdrawal	POLAR Main Study Database
t_{prn}	Documentation of Death / End of Study *(Primary Endpoint Assessment)*	Detailed Death Form	POLAR Main Study Database

Refer to the POLAR CRF Completion Guidelines for detailed instructions on data entry and how to complete each form.

10.0 Study Intervention

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.

Randomisation (Refer to Section 8.3 above) 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 will occur immediately prior to 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 (Static or Dynamic) should be displayed adjacent to the manometer.

10.1 General Delivery Room Management

10.1.1 Use of Regional Resuscitation Guidelines

The study intervention relates to the PEEP strategy used during stabilisation in the first 20 minutes after birth. Other aspects of delivery room care are standardised between the two groups unless detailed below.

Stabilisation/resuscitative care must be delivered in accordance with local guidelines (e.g. Neonatal Resuscitation Program (NRP), European Resuscitation Council, and Australian Resuscitation Council). Specifically, the following interventions are permitted during the intervention period or afterwards in the delivery room/NICU 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).

10.1.2 Method of Delivering Respiratory Support

Consistent with NRP guidelines on the stabilisation/resuscitation of newly born infants at birth, any respiratory support will commence initially by using CPAP via a non-invasive interface. The

POLAR Trial does not mandate the type of non-invasive interface, as long as it can deliver a PEEP range of 5-12 cmH_2O reliably - this includes facemask, nasopharyngeal tube, or nasal prong.

In both trial groups, the intervention is applied using a T-piece resuscitator device that delivers manually set pressure levels via a constant bias flow of gas, such as a Neopuff™ Infant Resuscitator.

- The bias flow rate must be set to ensure the PEEP levels can be maintained
- This should be confirmed during the 'Team Huddle' (Refer to Section 8.2 above)
- The clinician can 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.

In addition, the inflating pressure (PIP) and maximum pressure levels should be confirmed prior to commencing respiratory support. If this cannot be done beforehand, then the airway provider or an assistant should confirm the correct PIP and maximum pressure levels are correctly set as soon as possible after commencing respiratory support.

If an infant is intubated (Refer to Table 7 below), respiratory support can be delivered in the delivery room using the T-piece resuscitator or a mechanical ventilator at the site's discretion (Refer to Section 10.4). 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).

10.1.3 Delivery Room Monitoring

SpO_2 and heart rate using pulse oximetry or ECG are the most widely used physiological parameters to guide respiratory support needs, as more sophisticated methods of guiding respiratory care in the DR are lacking. The resuscitation team must assess respiratory effort, peripheral oxygen saturation (SpO_2) and/or heart rate response using pulse oximetry (right hand; pre-ductal) and/or ECG electrodes, during the intervention period, as per local site practice/policy.

Current NRP guidelines recommend continuous pulse oximetry, with heart rate assessment every 60 seconds. Consistent with these NRP recommendations, reassessment of the effectiveness of interventions should be made every 60 seconds, (more frequently if clinically appropriate or it is standard local practice to do so).

10.1.4 Definition of Respiratory Deterioration

The following criteria to monitor infant responses and define a ***respiratory deterioration*** (Refer to Table 7 below) that would require an escalation of the allocated intervention. Table 7 also describes the additional resuscitative measures that should be implemented in a stepwise order common to both intervention groups (similar to the MR SOPA approach used by the NRP).

Table 7: 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 **after 2 minutes**

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).

10.1.5 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 described in Table 8 below, defines failure of non-invasive support and the criteria to initiate intubation and placement of an endotracheal tube for PPV during the intervention period in the Delivery Room once highest permissible PEEP has been delivered.

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.

Table 8: 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 other interface (Refer to Section 6.1 above)

  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 above)

  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.**

10.2 Respiratory Support (PEEP) Strategies – Static and Dynamic

Refer to Section 7.0 of the POLAR Trial Protocol.

10.6 BPD Assessment at 36-week PMA

Assessment of BPD status (modified Walsh Test +/- standard oxygen reduction test) should be performed on the date determined to be 36+0 to 36+6 weeks corrected gestational age.

-
- 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 at 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. The assessment should be performed in conjunction with clinical assessment of BPD for local or regional reporting practices (e.g., VON, ANZNN). If local/regional reporting requires additional/alternative methods of assessing BPD (e.g., the Shift Test), these should still be conducted, and uploaded into the POLAR Trial REDCap database within the "36-week CGA BPD Assessment" CRF.

Refer to the POLAR CRF Completion Guidelines for detailed instructions on how to complete the "36-week CGA BPD Assessment" CRF.

10.6.1 BPD Assessment Criteria

The BPD assessment criteria detailed below must be completed for all infants enrolled in the POLAR trial, who reach the 36-week PMA time point.

For infants transferred to another hospital prior to 36 weeks PMA, the primary birth site/enrolling site is responsible for obtaining BPD assessment data and ensuring the correct assessment is performed.

Details of the BPD assessment protocol and air test have been pre-programmed into the "36-week CGA BPD Assessment" CRF within the POLAR Main Study Database. The CRF also includes the following features:

- Outlines instructions on completing the BPD assessment, determining if an infant requires an air test,
- Automatically diagnose whether an infant has BPD or does not have BPD; and
- Grades the severity of BPD using definition one (1) of Jensen et al AJRCCM 2019 (refer to Figure 1 within publication).

10.6.1.1 What to Do

- Perform this assessment on the date determined to be 36+0 to 36+6 weeks corrected gestational age.
  - If the BPD assessment cannot be performed during this time period, it is recommended that it be performed as soon as practical after 36+6 weeks corrected gestational age.

- Using the flow diagram below (refer to Figure 1 above) and starting from the level of respiratory support being applied, determine whether a room air trial (i.e., oxygen reduction test) is required. The CRF will also prompt you to the need for a room air test (oxygen reduction test).

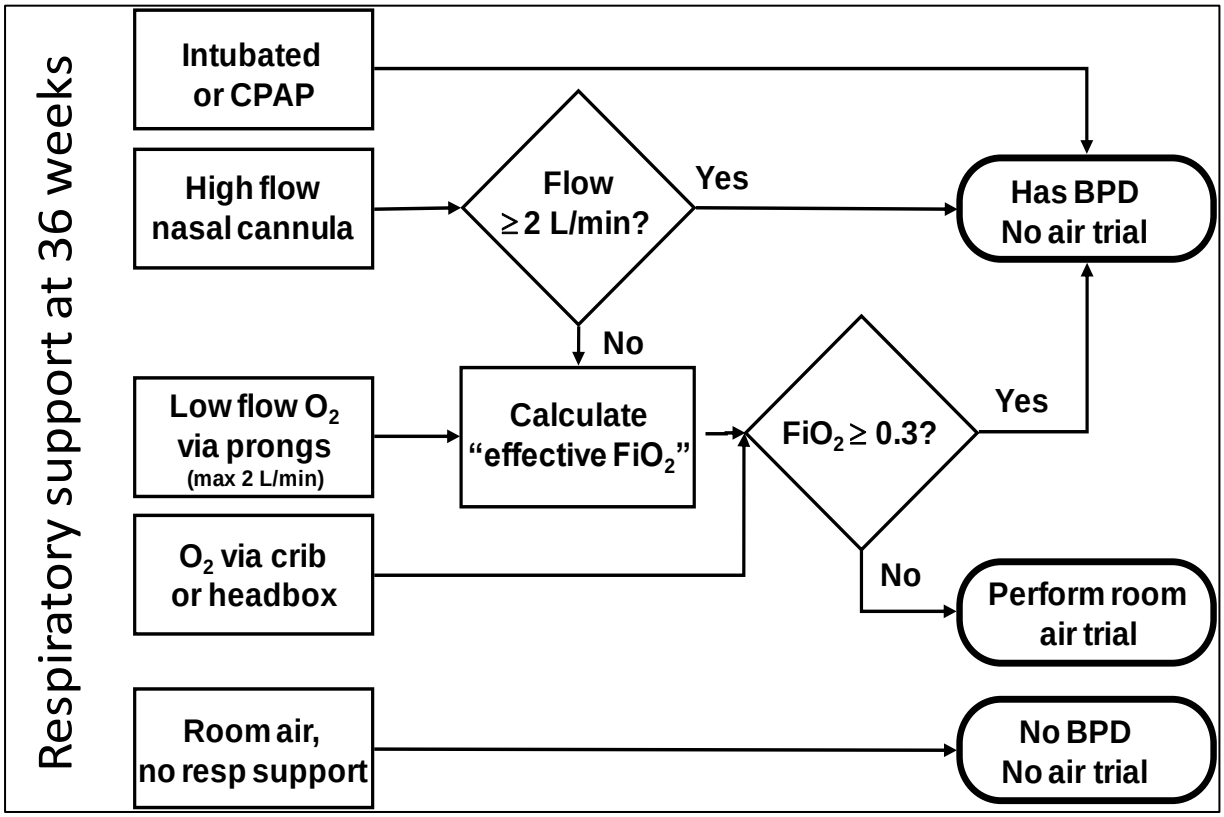
- If prompted, determine the "effective FiO_2". The following website, *Effective FiO_2 Conversion for Infants on Nasal Cannula* (https://urresearch.rochester.edu/institutionalPublicationPublicView.action?institutionalItemId=2913) provides a conversion tool for determining the effective FiO_2.

- Download the StopFiO2_js.htm file from the above website link, and enter:
  - Infant's current weight (in grams)
  - Oxygen concentration (as a percentage); and
  - Gas flow rate (liters per minute)

- Then enter the "effective FiO2" obtained into the CRF.

- If prompted, carry out a room air trial/oxygen reduction test and complete the relevant remaining sections of the CRF as outlined below.

Figure 7: BPD Assessment Flow Chart



10.6.2 Standard Oxygen Reduction Test

For infants with an effective FiO_2 >0.3 and delivered flow rate <2 L/min (not CPAP or support via an ETT) the criteria for a standard oxygen reduction test ('room air trial') will have been met. This should be conducted as follows:

10.6.2.1 How to Perform the Oxygen Reduction Test (Only if Effective FiO_2< 30%)

- Conduct the trial when the infant is in a quiet sleep if possible. Time the trial such that it will not coincide with the need to offer oral feeds, or other planned interventions.

- Continuously monitor the oxygen saturation (SpO_2) and pulse rate using a standard oximeter with alarms set at SpO_2 89% (lower) and 95% (upper)

- For the purposes of this oxygen reduction test, the acceptable SpO_2 target range will be **90-94%** before the trial.

- During the physiological evaluation, all infants should **ONLY** continue to the next FiO_2 or gas flow reduction step if SpO_2 is >=90% during the 5-minute monitoring phase.
- **STOP CRITERIA:** Immediately discontinue if SpO_2 are < 90% for 5 continuous minutes, or < 80% for 15 seconds or more (good quality oximetry signal) or apnoea or bradycardia >20 s. The infant should immediately be placed back in baseline oxygen and/or flow settings and the Oxygen Reduction Test recorded as a **FAIL**.

- **PASS** = maintenance of SpO_2 within the target range in room air for 30 minutes from the time of cessation of oxygen therapy.

- **FAIL** = Failure is defined as SpO_2 < 90% for 5 continuous minutes, or < 80% for 15 seconds or more (good quality oximetry signal) or apnoea or bradycardia >20 seconds.

- Oxygen therapy +/- respiratory support should thereafter be reinstituted irrespective of the test outcomes.

- The results of the room air trial should be shared with the treating clinicians.

METHOD:

a) If on nasal cannula (high or low flow) with oxygen blender:
Make stepwise 2% reductions in FiO_2 every 5 minutes, aiming to reach air within 20 minutes. If SpO_2 is still within the 90-94% target range, then stepwise reduce gas flow gradually to zero (0.5 LPM increments until flow 0.5 LPM, then 0.1 LPM reductions). If SpO_2 remains within the target range, gently **remove the prongs** from nares (but not face) and monitor for 30 minutes in room air (or 15 minutes if SpO_2 >=96% for 15 continuous minutes).

b) If on low flow prong (100% oxygen concentration, no blender):
Make stepwise reductions in the gas flow every 5 minutes aiming to reach zero flow within 20 minutes (e.g., 0.5 LPM increments until flow 0.5 LPM, then 0.1 LPM reductions). If flow metre allows further wean, decrease flow rate (e.g., in 0.02 LPM increments) every 5 minutes to lowest deliverable flow rate. If SpO_2 remains within the target range, gently **remove the prongs** from nares (but not face) and monitor

for 30 minutes in room air (or 15 minutes if SpO_2 >=96% for 15 continuous minutes).

c) If receiving oxygen via isolette (crib) or headbox:
Make stepwise reductions in FiO_2 by 2% every 5 minutes until room air. Monitor for 30 minutes in room air (or 15 minutes if SpO_2 >=96% for 15 continuous minutes).

10.7 Follow-Up Assessment at 24-Month

A follow-up visit will occur at 24-months corrected gestational age (+/- 2 months) to assess for respiratory and neurological outcomes if this is standard of care practice for the site.

The Research Coordinator/Member of the Clinical Care Team, or other appropriately qualified and trained staff, may obtain follow-up data so that the necessary outcome data (including death) is collected via the following methods:

- Consultation of the participants' medical records to obtain the required information
- Complete the assessment via a return in-person visit to the site.

If these data cannot be obtained from the medical records or if the participant does not attend for an in-person visit, a telephone consultation (e.g. via telehealth) with parent(s) may be completed, if this is standard of care practice for the site and when in-person visits are not able to be performed.

Refer to the Follow-Up Manual for detailed information and instructions on how to complete Follow-Up Assessments.

11.0 Adverse Event Reporting and Recording

Adverse events will be monitored during the study to ensure timely detection of events that may affect safety or continued participation.

11.1 Definitions

Refer to Section 11.1 of the POLAR protocol for current safety definitions observed for this trial.

11.2 Protocol-Defined Adverse Events and Serious Adverse Events

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

Table 10 and 11 below illustrates protocol defined AEs ad SAEs and the time frame in which must be reported:

Table 10: Protocol-Defined Specific 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.**

Table 11: Protocol-Defined Specific SAEs

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 tubes 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

The above AEs and SAEs occurring in each specified time frame must be recorded directly on the Adverse Event CRF within the POLAR Main Study Database.

Additionally, should any of the above protocol-defined AEs and SAEs occur beyond the specified reporting time frame, they must also be documented on the Adverse Event CRF within the POLAR Main Study Database, only if deemed related or possibly related to the study intervention, as assessed by the Site Investigator.

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

Note: Stillbirths do not need to be reported as SAEs.

11.2 Documentation and Reporting of AEs and SAEs

11.2.1 Documentation of AEs

For the purposes of this study, the Site Investigator is responsible for recording all protocol-defined adverse events only, regardless of their relationship to study intervention, 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/Grade (mild, moderate, severe, life threatening, fatal)
- Seriousness (i.e., is it an SAE?)
- Action taken, (i.e., none, intervention ceased, intervention delayed)
- The outcome (recovery, death, continuing, worsening)
- The likelihood of the relationship of the AE to the study intervention (Unrelated, Unlikely, Possible, Probable, Definite).

11.2.2 Reporting of Adverse Events

All protocol-defined 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 protocol-defined AEs (refer to Table 10 and 11 above) occurring in each specified time frame are to be recorded on the Adverse Event (AE) CRF within the POLAR Main Study database.

In addition, if any of the protocol-defined AEs occur beyond the specified time frame, they must also to be recorded and entered in the POLAR Main Study database, if deemed related or possibly related to study intervention, as evaluated by the Site Investigator/s.

11.2.3 Reporting of Serious Adverse Events

SAEs and USMs that occur from the time a participant has signed the informed consent form or is randomised (in situations of waiver of prospective 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 as outlined above.

SAEs and USMs must be submitted to the Sponsor c/o the Trial Coordinating Centre, using the POLAR Expedited Safety (SAE) Report Form*. Information recorded on this form will include:

- Verbatim term of the event
- Brief description/nature of the event
- Date of onset
- Severity/Grade (mild, moderate, severe, life threatening, fatal)
- Date of resolution (if event not ongoing)
- Date of notification to Medical Monitor
- Action taken
- Date of Death (if applicable)

**A copy of Expedited Safety (SAE) Report Form is available via the Members Portal area of the POLAR Website.*

Completed and signed Expedited Safety (SAE) Report Forms must be emailed to the following address:

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

All SAEs will be reviewed by the POLAR Medical Monitor within 24 hours of receipt. The Medical Monitor will review the Expedited Safety (SAE) Report Form, determine the relatedness and expectedness, and return a signed review form to the Trial Coordinating Center for record keeping. Should the Medical Monitor have any questions for the site regarding the SAE, the Trial Manager will contact the participating site directly via email for clarification.

All SAEs will be reported to the DSMC during regularly scheduled meetings. The Medical Monitor will report any significant intervention-related SAEs or safety events of concern (i.e., USMs, SSIs, and URSAEs) to the DSMC immediately if deemed necessary. Human Research Ethics Committees/Institutional Review Boards should also be notified according to the policies of each institution.

12.0 Data Management

This section describes requirements for data collection, data entry, and submission of de-identified/redacted source documents from enrolled participants, how to gain access to the POLAR electronic data capture (EDC) platform i.e., the Trial Databases, and the data review, data cleaning and data Quality Assurance (QA) process.

12.2 Electronic Data Capture (EDC) – The POLAR Trial Database

A secure REDCap (Research Data Capture) electronic data capture (EDC) platform is provided for the entry and storage of clinical trial data. REDCap is a secure, web-based application for building and managing online survey and forms. Access to the POLAR REDCap database/s will be granted to individual site users by the DCCe Database Manager.

Research Team Members will enter trial data directly into the POLAR study database/s with the exception of Delivery Room (DR) data which will initially be captured on a paper CRF (i.e., Delivery Room Management paper CRF) and subsequently entered into the study database, for those sites wishing to use a paper CRF within the DR.

Participating Sites may wish to use their own site-specific/local version of a paper Neonatal Resuscitation Form or electronic Delivery Room data collection tool:

- If so, prior approval must be sought by the site for use of such methods to record DR data.
- A copy of the local Resuscitation Form/details of the electronic data collection tool MUST be provided to the POLAR Sponsor-Investigator or Trial Manager prior to site activation for review and approval.
- If a site has been granted approval to use a local version of their paper Resuscitation Form or electronic Delivery Room data collection form, then the same principles as outlined above must be applied.

Designated and authorised site staff must complete the CRFs and supporting documentation for each participant within a timely manner of each assessment occurring. Staff delegated by the Site Principal Investigator to enter data must be indicated on both the Site Signature and Delegation of Authority Log and Training Log, prior to granted being access to the study database/s.

12.2 Database Training and Resources

All site staff responsible for data collection and data entry into the POLAR study database must be identified on the Site Signature and Delegation of Authority Log and Training Log and must attend the Site Initiation Meeting (where applicable), whereby specific EDC training will be provided as part of the presentation.

Whilst there is no additional study-specific online EDC training certification or requirements for data entry staff, it is expected that site staff responsible for data collection and data entry thoroughly read and 59amiliarize themselves with the following training resources provided:

a) POLAR Protocol – current version
b) POLAR CRF Completion Guidelines
c) REDCap Data Entry User's Guide & Reference Manual
d) POLAR Site Initiation Presentation Slide Set – Data Management & Data Entry Section (i.e., Section 3.0)
e) POLAR Manual of Procedures – Section 12; Data Management

12.3 Acquiring Access to the REDCap Database/s

A unique REDCap username and password is required for ***each*** site staff member who will be entering data or who will require access into the POLAR study databases. Each designated research team member must complete and submit a REDCap Access Account Application Form, in order for a username and password to be issued.

1. Complete the EDC Access Account Application Form *[Available via the Member's Portal or by contacting the POLAR Trial Manager]*
2. Email completed forms to: POLAR@mcri.edu.au
3. You will be notified by the Data Coordinating Centre when your account has been created and be provided with a username and password.

To ensure data security and confidentiality, it is of utmost importance that your individual username and password not be shared among site staff members. Data integrity and use of the REDCap database will be tracked through the log feature in the electronic data capture system. When changes are made to the data within the system it will be tracked via each individual's username.

12.4 Data Entry

All CRFs will be completed electronically and entered directly into the POLAR REDCap database, with the exception of, the "Delivery Room Management*" CRF, for sites wishing to capture DR parameters manually.

The Delivery Room Management CRF has been designed as a paper CRF, to allow real-time recording of key clinical and physiological data points used in the NRP algorithm, by the Delivery Room Team 'scribe'. The Delivery Room Management paper CRF will then be entered into the trial database along with the remaining data collected at the same time point.

Refer to Section 7.5 of the POLAR CRF Guidelines for an annotated Delivery Room Management CRF and detailed instructions on how to complete the paper form.

Completion of data entry into REDCap must be completed **within 5 business days** of the participant's birth and/or assessment date or within 5 business days of when the results of any completed investigations/assessments are available, to prevent the accumulation of un-entered forms.

Data Manager/s at the Data Coordinating Centre (DCCe) will review the data for accuracy and completion.

**A copy of Delivery Room Management CRF is available on the POLAR Website and will also be provided within each Randomisation Envelope.*

12.5 Data Cleaning, Validation and Queries

Through a variety of data and range checks, REDCap helps prevent inconsistencies or invalid data. The trial database will check for the following errors:

1. Data fields that are out of range
2. Inconsistent or illogical entries
3. Incompleteness or missing data, and
4. Numerical values that are far outside the range of those previously entered.

Data Managers will raise relevant queries within the trial database regarding any errors identified, in order to resolve any inconsistencies. Sites should make every attempt to address and resolve raised queries in REDCap within 5 business days.

Data Managers will also review data entered into REDCap against any de-identified source documents submitted to the DCCe to validate and confirm data entry. Refer to Section 12.6 below for a complete list of de-identified source documents required for submission.

We will maintain a record of changes to the REDCap database. Database errors include:

1. Missing data
2. Implausible data
3. Erroneous data; and
4. Errors arising from difficulties with the electronic CRFs themselves.

Weekly data metric and quality assurance reports will summarise the number of each of these including the number of outstanding queries at sites. Most importantly, we will closely monitor the time between study visits and submission of the electronic CRFs into REDCap to ensure that this time is less than 5 days. If entry times exceed 5 days, then this will trigger a response, which may include investigation, retraining, and potentially reassignment.

12.6 Source Document Plan & Submission Checklist

Source data and methods of capture of source data must be clearly defined prior to randomisation of the first participant. Sites must identify the location of source documents at site by completing the POLAR Source Document Plan & Submission Checklist. This checklist should be prepared by each participating center and signed and dated by the principal investigator.

12.6.1 What are Source Documents?

Source documents are documents which contain source data. Source data is defined as: "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." [*Section 1.51, Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA Comments*].

Examples of electronic or hardcopy documents that contain source data can include:

- Medical Records / Electronic Medical Record
- Participant Diaries
- Recorded data from automated instruments (e.g., blood pressure measurement)
- Participant - or researcher-completed questionnaires or rating scales
- Hospital Discharge Summaries
- Pharmacy Dispensing Logs and other records
- Laboratory Results
- ECGs and Reports
- Radiological Reports
- Autopsy Reports
- Death Certificates

12.6.2 Why are Source Documents Important?

Source documents will be used to:

1. Confirm the study participant exists
2. Confirm the reported study data is accurate (data integrity)
3. Confirm the study is conducted according to the protocol (study compliance).
4. Confirm compliance with Principles outlined in the following:
   - National Statement on Ethical Conduct in Human Research
   - Australian Code for the Responsible Conduct of Research
   - Notes for Guidance on Good Clinical Practice (GCP)
   - Royal Children's Hospital Research Ethics and Governance procedure 'Investigators' Responsibilities in Research'.

12.6.3 Submitting your Completed Checklist

Each site must identify the location of your source data in accordance with the data variables listed in the POLAR Source Document Plan & Submission Checklist* and provide a completed and signed site-specific plan to the Trial Manager prior to holding your Site Initiation Meeting.

Completed Source Document Plans are to be submitted via email to the POLAR Data Coordinating Centre (DCCe), c/o the POLAR Trial Manager: POLAR@mcri.edu.au

The original copy of the form must be filed within your site-specific POLAR eISF eBinders™ folder.

**A template copy of the Source Document Plan & Submission Checklist can be found on the POLAR website.*

12.7 Submission of De-Identified / Redacted Source Documents

In accordance with the POLAR Source Document Plan and Submission Checklist, the following de-identified/redacted source documents are required for submission at various time points throughout study conduct:

Table 12: De-Identified/Redacted Source Documents Required for Submission

Outcome Measure / Data Point	Time Point	Data Completion or De-Identified Source Document Required for Submission
Delivery Room Management	Time of Birth	1. Delivery Room Management CRF (paper CRF) or your local Hospital Resuscitation Form/Code Sheet, whichever is used to document DR data.
BPD	36-Week CGA BPD Assessment	1. Hardcopy of any Modified Walsh Test, Standard Oxygen Reduction Test Report or other BPD Assessment Tool retained in participants medical record or submitted to regional Neonatal Network Database, if available. (e.g., VON, ANZNN).
Death	If occurs	1. Birth Hospital's Discharge Summary and/or Receiving Hospital's Discharge Summary
		2. Death Certificate (if available), or copy of participants Medical Record notes confirming Date of Death
		3. Autopsy Report, if applicable
		4. Radiological Report, if applicable
		5. ECHO Report, if applicable
		6. Coroner's Report, if applicable

12.7.1 Submitting Source Documents to the DCCe

1. Source documents are submitted to the POLAR Data Coordinating Centre (DCCe) by uploading a PDF of the document directly into the Florence eBinders using the "upload file" function.

2. Ensure any **identifying information,** including participant names, addresses, patient hospital numbers, provider information etc., **have been completely removed/redacted –** this can be completed prior to uploading any documents into Florece eBinders, or by using the in-built "redaction" tool within Florence.

3. Ensure the Participant Identification Number (PID#) is clearly visible on the top right-hand side of the source document.
   - You can add text to a document uploaded in Florence using the in-built "annotate" tool.

4. Refer to the POLAR CRF Completion Guidelines [Section 3.8] for further instructions on uploading source documents into Florence eBinders.

13 Quality Control, Compliance Monitoring and Trial Monitoring

The Trial Coordinating Centre (TCC) will evaluate and monitor the quality of study activities and the integrity of data quality through establishing a number of quality control measures to review and assess compliance to protocol intervention, primary endpoints, adverse events and data reporting accuracy and standards.

13.1 Study Endpoint Adjudication Committee (SEAC)

A Study Endpoint Adjudication Committee (SEAC) has been established to remotely monitor, evaluate, and classify death events and assess whether the death may have been related to trial intervention.

The SEAC is a sub-committee of the Data Safety Monitoring Committee (DSMC) and will report directly to the DSMC and the Trial Steering Committee (TSC). The SEAC will be blinded to the study intervention and will meet quarterly to remotely monitor every mortality event reported throughout the study.

Redacted source documents will be monitored to confirm:

a) Confirm the date of death, as per source documents
b) Confirm the location/age of death, as per source documents
c) Assess the cause of the death and determine whether it was related to the intervention
d) Assess whether the Respiratory Management within the Delivery Room contributed to the death event
e) Assess whether there were any other potential contributing factors that may have played a role in the cause of death
f) Assess whether the death event represented a Safety Signal of concern for the study.

Sites should make every attempt to upload redacted or tagged (using the PHI tag functionality within the Florence eBinders Platform) source documents into Florence eBinders (Folder 13.6), as soon as they are available and within a reasonable and practical time, in order to facilitate monitoring of the event.

Should queries arise between the SEAC Monitors assessment of cause of death and the site's assessment of cause of death, the POLAR Trial Monitor will raise appropriate queries within the study database for the site to consider. Sites should make every attempt to address and resolve any queries raised within REDCap within 5 business days, as per Section 12.5 above.

13.2 Protocol Deviations / Events of Non-Compliance

All protocol deviations/events of non-compliance must be recorded in the participant's medical record (source document) and on the corresponding Protocol Deviation CRF within the POLAR Main Study database.

13.2.1 Assessment and Categorization of Protocol Deviations

The site principal investigator, or delegate, must categorise protocol deviations as either major or minor according to the following definitions:

Minor Deviations:

Minor protocol deviations are 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 are 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 of 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.

Reportable major protocol deviations include but are not limited to:

- Failure to follow randomised treatment arm assignment in delivery room resuscitation of enrolled infant
- Opening more than one randomization 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 (SAEs) to the Sponsor
- Continuing research activities after HREC/IRB approval has expired.

13.2.2 Submitting Expedited Reports of Major Protocol Deviations

Deviations categorised as major must be reported to the Sponsor c/o the Data Coordinating Centre within 24 hours of site staff becoming aware of the event.

Major deviations are reported using the POLAR Non-Compliance Report Form*. Completed forms must be emailed to the POLAR Trial Manager at: POLAR@mcri.edu.au

Based on the severity of the protocol deviation and institutional guidelines, the Sponsor will determine if the event requires reporting to the HREC/IRB (i.e., Serious Breach has occurred) or other ethical or regulatory bodies as appropriate. All protocol deviations will be reported and reviewed during scheduled DSMC and TSC meetings.

**A copy of Non-Compliance Report Form is available on the POLAR Website.*

13.3 Protocol Intervention Compliance Self-Assessment

Acknowledging that the Delivery Room can be a dynamic, fast-paced, and rather frantic environment, the risk of encountering deviations within the Delivery Room (DR) during administration of protocol-assigned intervention is far greater than your standard birth.

To assist sites with complying with the intervention and reduce and prevent recurring deviations and we have established a two-step review of protocol intervention compliance within the DR:

Step 1: Site completes its own internal self-assessment of the intervention delivered and of the procedures undertaken within the Delivery Room to determine whether the assigned algorithm was followed according to the protocol. The self-assessment is to be performed by a member of the research team who **was not** present at the birth of the infant.

Results of the internal self-assessment will be recorded by the site within the POLAR study database on the "Protocol Compliance Self-Assessment" CRF.

Step 2: An unblinded external Independent Medical Reviewer will review a selection of cases from each site to ensure compliance with the assigned intervention. The Medical Reviewer will also review the sites completed internal self-assessment and report any identified major deviations to the POLAR Trial Manager in a blinded fashion, in order to action accordingly.

To assist both the participating sites and the external independent Medical Reviewer in assessing protocol-compliance, a set of **Minor** and **Major** deviation criteria has been established, focusing on Delivery Room management.

Both the participating site and the independent Medical Reviewer will review compliance within the DR against this set of defined criteria.

Refer to Tables 13 and 14 below for Minor and Major protocol compliance deviation criteria.

Table 13: Minor Protocol Intervention Deviation Definitions:

MINOR DEVIATIONS	
BOTH GROUPS	Randomisation occurring after birth, and less than 1 minute after mask first placed on the face of the infant, as long as correct intervention is applied.
	Incorrect (or absent) use of airway corrective steps when respiratory deterioration criteria have been met.
	Delay in commencing PPV, if appropriate.
	PIP commenced at >25 cmH_2O.
	Interruption of intervention protocol by less than two minutes.
	Interruption of protocol intervention for a procedure.
	Delay in increasing or decreasing FiO_2 to meet SpO_2 target ranges (after the first 3 minutes of allocated respiratory support).

	Failure to monitor at least respiratory effort, heart rate and/or SpO_2 minutely in the Delivery Room.
	Failure to document at least CPAP level and FiO_2 on a minutely basis in the Delivery Room.
STATIC GROUP	Delivery of PEEP >6 cmH_2O for less than 2 minutes (120 seconds) in the Delivery Room.
DYNAMIC GROUP	Delay in increasing or decreasing PEEP value as per protocol for less than 4 minutes after clinically indicated.
	Delivery of PEEP <8 cmH_2O for less than 2 minutes (120 seconds) in the Delivery Room.
	Increasing or decreasing PEEP too rapidly.

Table 14: Major Protocol Intervention Deviation Definitions:

MAJOR DEVIATIONS	
BOTH GROUPS	Randomisation occurred more than 1 minute (60 seconds) after mask placed on face.
	Failure to administer randomised treatment group assigned.
	Failure to monitor respiratory effort, heart rate and/or SpO_2 during first 20 minutes after mask placed on face.
	Pulse oximetry or ECG never applied during management in the Delivery Room.
	Failure to identify or implement the Respiratory Deterioration protocol (Refer to Table 6.1 in Protocol) despite meeting criteria to do so.
	Intubation without applying the additional resuscitative measures detailed in Table 6.1 (at the highest permissible PEEP level).
	Not intubating the infant despite meeting the criteria to do so (Refer to Table 6.2 in the Protocol).
	Delivery of PIP at <20 cmH_2O (if criteria for PPV is met), unless commenced at 20 cmH_2O or above and weaned due to clinical improvement.
	Delivery of PIP at >25 cmH_2O after evidence of clinical improvement at the higher PIP (Refer to Table 6.1, point number 3, in the Protocol).
	Interruption of allocated intervention for more than 2 continuous minutes (unless for a procedure).
	Failure to administer any Intervention
STATIC GROUP	Delivery of PEEP of 7 cmH_2O or more for 2 minutes or more in the Delivery Room.
	Delivery of PEEP of <5 cmH_2O for 2 minutes or more in the Delivery Room.
	Use of PEEP other than 5-6 cmH_2O after intubation.
DYNAMIC GROUP	PEEP of 7 cmH_2O or less provided from more than 2 minutes (120 seconds) at any time in the Delivery Room.
	PEEP never escalated from 8 cmH_2O despite meeting criteria to do so.
	Delivery of PEEP of >12 cmH_2O at any time in the Delivery Room.

	Failure, or at least a 4 minute delay in increasing to the next PEEP level, as required per protocol, when respiratory deterioration criteria have been met.
	Failure, or at least a 4 minute delay, in decreasing to the next PEEP (if >8 cmH_2O) if HR >100 bpm or FiO_2 <0.30 (for at least 60 seconds).
	Intubation prior to effective PPV delivered for at least 60 sec at PEEP of 12 cmH_2O.
	Use of PEEP other than 8 cmH_2O after intubation.

Refer to the POLAR eCRF Completion Guidelines for further information on how to complete the "Protocol Compliance Self-Assessment" CRF.

13.4 Remote / Central Monitoring

This study will include risk-based remote/central monitoring, and where required, for-cause on-site monitoring visits.

Risk-based remote/central monitoring will involve:

- Routine review of essential documentation e.g., Signature and Delegation of Authority Logs, Training Logs, GCP Training Certificates, PEEP Training Attestation forms, Screening data within the POLAR Screening Database, and remote monitoring via the Florence eBinders™ platform
- Centralised review of eCRFs for data accuracy and completeness
- Source data verification of redacted Source Documentation uploaded into Florence eBinders for data accuracy and completeness
- Review of data-entry timelines and response to query timelines
- Protocol Compliance Review within the DR by the external Medical Reviewer
- Mortality monitoring of death events reported

13.5 On-Site Monitoring / For-Cause Site Visits & Audits

According to ICH-GCP Guidelines, the Sponsor may monitor the participating site to compare raw data, source data/documentation and associated records with the interim (if applicable) or the final report of the trial to assure that data have been accurately reported. The Sponsor is responsible for the auditing of the trial. Site monitoring may be contracted to an external body. The Investigator(s) must accept that regulatory authorities may conduct an audit or inspection to verify compliance of the trial with ICH-GCP.

In cases where on-site monitoring is required, the monitor will attend sites based on the needs and requirements of the trial, as determined by the Sponsor and in accordance with the POLAR Clinical Monitoring Plan.

The Monitor or Sponsor Representative is responsible for ensuring that the trial is conducted according to Standard Operating Procedures (SOPs) to ensure compliance with ICH-GCP. The Monitor is the primary link between the Sponsor and the Investigator. The main responsibilities of the Monitor are to visit the Investigator before during and after the trial to ensure adherence to the protocol, and to assure that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all participants within the trial.

The Monitor will be allowed access to check and verify the various records (CRFs and other pertinent data records) relating to the trial to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. As part of the supervision of the trial progress other Sponsor personnel may, on request, accompany the Monitor on visits to the trial site. The Investigator and assisting staff must agree to cooperate with the Monitor to resolve any problems, errors, or possible misunderstandings concerning any data discrepancies detected in the course of these monitoring visits. By signing the informed consent form, the participant gives the authorised Monitor direct access to participant's medical records and the study data.

The Trial Manager will contact each participating site to arrange a mutually suitable time for for-cause on-site monitoring visits, should visits be deemed required.