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Extubation CPAP Level Assessment Trial (ÉCLAT): In extremely preterm infants <28 weeks' gestation, undergoing their first extubation, does extubation to a higher CPAP pressure (10 cm H2O, range 9-11 cm H2O), compared with a standard CPAP pressure (7 cm H2O, range 6-8 cm H2O) decrease extubation failure within seven days?

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Title Page

Title:

Extubation CPAP Level Assessment Trial (ÉCLAT): In extremely preterm infants born <28 weeks' gestation, undergoing their first extubation, does extubation to a higher CPAP pressure (10 cm H_2O, range 9-11 cm H_2O), compared with a standard CPAP pressure (7 cm H_2O, range 6-8 cm H_2O) decrease extubation failure within seven days?

Authors

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Trial Registration

Australia and New Zealand Clinical Trial Registry: ACTRN12618001638224

Keywords:

Extremely preterm, infant, endotracheal extubation, continuous positive airway pressure.

Data sharing statement:

The protocol will be published and publicly available, and the de-identified individual patient datasets and statistical codes will be available on reasonable request.

Word count: 2604

Abstract

Introduction: Respiratory distress syndrome (RDS) is a common complication of prematurity and extremely preterm infants born before 28 weeks' gestation often require endotracheal intubation and mechanical ventilation. In this high-risk population, mechanical ventilation is associated with lung injury and contributes to bronchopulmonary dysplasia (1). Therefore, clinicians attempt to extubate infants as quickly as possible and use non-invasive respiratory support such as nasal continuous positive airway pressure (CPAP) to facilitate the transition. However, approximately 60% of extremely preterm infants experience 'extubation failure' and require re-intubation (2). Whilst CPAP pressures of 5-8 cm H_2O are commonly used after extubation, the optimal CPAP pressure is unknown (3), and higher pressures may be beneficial in avoiding extubation failure.

Methods and analysis: A total of 200 infants born extremely preterm will be recruited prior to their first attempted extubation from mechanical ventilation to CPAP. Infants will be randomly assigned to one of two set CPAP pressures: CPAP 10 cm H_2O (intervention) or CPAP 7 cm H_2O (control). The primary outcome will be extubation failure (re-intubation) within seven days.

Ethics and dissemination: Ethics approval has been granted by the Monash Health and Royal Women's Hospital (Melbourne, Australia) Human Research Ethics Committees. Any amendments to the trial protocol will be submitted to the ethics committees for approval. The trial is currently recruiting at these two sites. The findings of this study will be disseminated via peer-reviewed journals and presented at national and international conferences. This trial was prospectively registered with Australia and New Zealand Clinical Trial Registry (ACTRN12618001638224).

Article Summary

Strengths and limitations of this study:

- Strength: Randomised controlled trial
- Strength: The largest trial comparing CPAP pressure ranges to reduce extubation failure in extremely preterm infants
- Strength: CPAP pressures as high as 9-11cm H_2O are yet to be formally evaluated
- Strength: Multicentre trial
- Limitation: Unable to be blinded

Introduction

Respiratory distress syndrome (RDS) is common in preterm infants, and almost universal in extremely preterm infants born <28 weeks' gestation. In this high-risk population, bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, is a major morbidity following RDS and its treatment (4). Many extremely preterm infants require endotracheal intubation and mechanical ventilation (4). Mechanical ventilation, particularly if prolonged, injures the lungs and contributes to BPD (5). Consequently, avoiding or minimising the time that extremely preterm infants are mechanically ventilated is critical.

The optimal way to provide respiratory support to extremely preterm infants after mechanical ventilation remains under investigation, and the transition from mechanical ventilation to non-invasive respiratory support remains a poorly understood process (5). There is a paucity of data on the optimal timing of extubation, criteria for readiness for extubation, and the best strategy to use when providing post-extubation respiratory support (6). The extubation failure rate in extremely preterm infants is high, estimated at 60% (2), and reducing this outcome must be a focus of research.

Nasal continuous positive airway pressure (CPAP) is the most frequently used mode of non-invasive support used after extubation of extremely preterm infants. The reasons for extubation failure during CPAP are multifactorial. Variables such as infant weight (birth weight <750g), immaturity (<26 weeks' gestation) and the severity of RDS (alveolar-arterial gradient >180 mm Hg) are weakly predictive of early CPAP failure in very preterm infants (2). The use of a set CPAP pressure sufficient to maintain functional residual capacity is likely to be important (7). The optimal CPAP pressure to use after extubation is unknown, although a meta-analysis of studies suggests that pressures of at least 5 cm H_2O are needed (7). Many infants are re-intubated following extubation for increased oxygen requirement and work of breathing suggesting that a low end-expiratory lung volume may contribute to extubation failure (8).

Utilising higher CPAP pressures post-extubation may prevent alveolar collapse, improve lung function and reduce extubation failure (9,10). Kitsommart *et al* compared CPAP 7-9 cm H_2O with CPAP 4-6 cm H_2O after extubation of infants with birth weight <1250 g and demonstrated no difference in extubation failure within 72 hours (9). In a second trial, Buzzella *et al* randomised very preterm infants born 23-30 weeks' gestation with RDS to receive either CPAP 7-9 cm H_2O or CPAP 4-6 cm H_2O after extubation (10). Rates of extubation failure within 96 hours were significantly lower in the group randomised to the higher range of CPAP pressures (10). Current CPAP pressure recommendations are wide and varied (7). Most

clinicians report pressures of 5-8 cm H_2O however, use of CPAP pressures up to 12 cm H_2O have been reported and have not been associated with adverse effects (3).

In extremely preterm infants, extubation failure is associated with significant morbidities, including BPD, pulmonary vascular disease, airway trauma, poor feeding and oral aversion, adverse neurodevelopmental outcomes, and delayed family unit bonding (11). Thus, improving rates of successful extubation in this high-risk population of preterm infants is a clinical priority (1,11–14). The ÈCLAT trial will investigate the CPAP pressure range of 6-8 cm H_2O, routinely used in our clinical practice, with a higher-pressure range of 9-11 cm H_2O. We hypothesise that the higher-pressure range will result in less atelectatic pulmonary failure and extubation failure.

Methods and analysis

Study design and aim

We used the APIRIT checklist when writing our report (15). This is a multicentre, unblinded, randomised controlled trial. The aim of the ECLAT study is to determine, in extremely preterm infants born <28 weeks' gestation who are undergoing their first extubation, whether extubation to a higher CPAP pressure (10 cm H_2O, range 9-11 cm H_2O), compared with a standard CPAP pressure (7 cm H_2O, range 6-8 cm H_2O) decreases extubation failure within seven days.

Sample size

The rates of extubation failure within 7 days in extremely preterm infants at the participating centres is estimated at 55%. To detect a reduction in extubation failure from 55% to 35% (absolute risk reduction 20%, relative risk reduction 40%) with 80% power and a two-tailed alpha error of 0.05, a sample size of 93 infants in each arm (total 186 infants) is required.

Patient population

Infants born extremely preterm (<28 weeks' gestation) who are intubated and mechanically ventilated and being extubated for the first time are eligible for participation in the ÉCLAT trial. The timing of the extubation is determined by the clinical team caring for the infant, and there is no postnatal age limit for participation.

Inclusion criteria

Infants are eligible if they:

- were born <28 completed weeks' gestation

- are being extubated for the first time from mechanical ventilation to nasal CPAP
- have received enteral or intravenous caffeine (as prophylaxis for apnoea of prematurity) <24 hours prior to the planned extubation
- have received exogenous surfactant treatment.

Exclusion criteria

Infants are excluded if they:

- are being extubated to any other mode of non-invasive respiratory support other than nasal CPAP, or to no respiratory support
- have a major congenital anomaly or condition that might adversely affect breathing or ventilation: e.g. known upper airway obstruction or major airway abnormality, or major congenital heart disease
- are not receiving full intensive care after extubation.

Randomisation

Enrolled infants are randomised using REDCap electronic data capture tools (16), hosted at the Murdoch Children's Research Institute, Melbourne, Australia. REDCap (Research Electronic Data Capture) is a secure, password encrypted, web-based application designed to support data capture and randomisation for research studies. Only the infant's first extubation is randomised. Multiple births are randomised individually. Randomisation occurs after the clinical decision to extubate has been made and shortly before extubation using a computer or smartphone. Stratification is by centre and gestational age at birth (<26 weeks; ≥26 weeks).

Clinical Management [Figure one]

Higher CPAP pressure (Intervention)

Infants are extubated to a set CPAP pressure of **10 cm H_2O**. Whilst receiving CPAP, infants will remain within a set CPAP pressure range of **9 cm H_2O – 11 cm H_2O** for at least **24 hours,** with changes within this range at the discretion of the treating team. After 24 hours, infants may have their set CPAP pressure weaned at the discretion of the treating team but must remain within a set CPAP pressure range **5 cm H_2O – 11 cm H_2O** for at least **7 days** after extubation if receiving CPAP. Infants are re-intubated if they satisfy the extubation failure criteria

described below within 7 days after extubation. The fraction of inspired oxygen (FiO_2) is titrated to keep oxygen saturations (SpO_2) in the standard target ranges of the participating unit. If extubation failure occurs, management following re-intubation will be at the discretion of the treating team. For subsequent extubations, clinicians will be encouraged to use the assigned set CPAP pressure range (see figure one).

Standard CPAP pressure (control)

Infants are extubated to a set CPAP pressure of **7 cm H_2O**. Whilst receiving CPAP, infants will remain within a set CPAP pressure range of **6 cm H_2O – 8 cm H_2O** for at least **24 hours,** with changes to the set CPAP pressure within this range at the discretion of the treating team. After 24 hours, infants may have their set CPAP pressure weaned at the discretion of the treating team but must remain within a set CPAP pressure range **5 cm H_2O – 8 cm H_2O** for at least **7 days** after extubation if receiving CPAP. Infants are re-intubated if they satisfy the extubation failure criteria described below within 7 days after extubation. The FiO_2 is titrated to keep SpO_2 in the standard target ranges of the participating unit. If extubation failure occurs, management following re-intubation will be at the discretion of the treating team. For subsequent extubations, clinicians will be encouraged to use the assigned set CPAP pressure range (see figure one).

Device

In both groups, infants will be extubated to continuous-flow nasal CPAP, via a mechanical ventilator (either the Dräger VN500, Dräger Medical, Lübeck, Germany, or the SLE 5000, SLE, Croydon, UK) operating in CPAP mode. After 24 hours the infant may be transitioned to 'bubble' nasal CPAP (Fisher & Paykel bubble CPAP circuit, Fisher & Paykel Healthcare, Auckland, New Zealand) but only if receiving a CPAP $\leq$ 10cmH_2O given the pressure limitations of the 'bubble' CPAP device. Nasal CPAP may be delivered via any binasal CPAP prongs or mask, according to the participating unit's protocol.

Outcomes

Extubation Failure

The primary outcome is extubation failure within 7 days, defined as receiving the *maximum* CPAP level (11 cm H_2O in the intervention group; 8 cm H_2O in the control group) and having at least one of:

- FiO_2 requirement >0.20 above the pre-extubation FiO_2
- Two or more apnoeic episodes within any 24-hour period requiring intermittent positive pressure ventilation, or six or more apnoeic events requiring stimulation in any 6-hour period
- Respiratory acidosis with pH <7.2 *and* pCO_2 >60 mm Hg
- Require urgent intubation for an acute deterioration (at clinical discretion) with the reason for re-intubation documented.

Treatment failure

Should infants not be immediately reintubated and instead managed with non-invasive positive pressure ventilation or escalated to a higher CPAP pressure than their assigned range they will be documented as an extubation failure and reported as a protocol violation.

Secondary outcomes

- Incidence of re-intubation within 72 hours, and within 96 hours
- Incidence of
- Failure in hours after extubation
    - Reason(s) for extubation failure
    - Kaplan Meier Survival curve between both groups
- Death before hospital discharge
- Duration of mechanical ventilation in days after randomisation in survivors
- Total duration of hospitalisation in days in survivors
- Postmenstrual age at last supplemental oxygen, and at last positive pressure ventilation (mechanical ventilation, CPAP [or variants], or nasal high-flow ≥2 Litres per minute) in survivors
- Incidence of treatment with systemic postnatal corticosteroids for lung disease after randomisation
- Incidence of new pneumothorax requiring drainage with thoracocentesis or intercostal catheter insertion after randomisation
- Incidence of new, radiologically-diagnosed pulmonary interstitial emphysema after randomisation

- Incidence of BPD, defined as a requirement for supplemental oxygen and/or respiratory support (mechanical ventilation, CPAP [or variants], or nasal high-flow ≥2 Litres per minute) at 36 weeks' post-menstrual age
- Incidence of necrotising enterocolitis Bell's stage 2 or above after randomisation (17)
- Incidence of spontaneous intestinal perforation after randomisation
- Incidence of retinopathy of prematurity requiring treatment with laser therapy or intra-ocular medication in one or both eyes after randomisation
- Incidence of new diagnosis of grade 3 or 4 intraventricular haemorrhage after randomisation

Other data

Data collected will include:

- Maternal and infant demographics: maternal parity, infant sex, gestational age at birth, birth weight in grams, mode of delivery, exposure to any antenatal corticosteroids, duration of ruptured membranes prior to delivery in days, presence of histologically diagnosed chorioamnionitis
- Postnatal age at extubation in days, last weight prior to extubation in grams, age at first intubation in hours
- Previous dose of exogenous surfactant received in milligrams/kilogram, prior treatment for a patent ductus arteriosus (pharmacological or surgical), prior systemic postnatal corticosteroids for lung disease
- Mechanical ventilator settings immediately prior to extubation (mode, mean airway pressure in mmHg, FiO_2, tidal volumes (set and achieved), peak pressures (set and achieved) and end expiratory pressure.
- Blood gas analysis results within 24 hours prior to extubation (if applicable): lowest pH, highest pCO_2, lowest base excess.

Data analysis plan

Statistical analysis will follow standard methods for randomised trials. For the primary outcome, the analysis will be by intention to treat and be adjusted for the pre-randomisation strata (GA and centre). For dichotomous outcomes, including the primary outcome, the two treatment groups will be compared using risk difference with 95% CI, both overall, and within the pre-specified subgroups (gestational age at birth <26 weeks, ≥26 weeks). For dichotomous

secondary outcomes, analysis will be limited to the two treatment groups, using risk difference with 95% CI. For continuous outcomes, the two treatment groups will be compared using difference of means, together with 95% CI, for outcome variables which are normally distributed; for outcome variables, which are not normally distributed, the comparison will be difference of medians, with 95% CI. All comparisons (risk difference, difference of means, difference of medians) will be estimated using regression models with the randomisation strata as covariates, and with standard errors adjusted to take into account the clustering due to multiple births. Reporting of findings will be done in accordance with CONSORT guidelines.

Ethics and Dissemination

Infants are only enrolled after prospective, informed, written parental consent. Parent(s) of eligible infants will be approached by a member of the research team. A verbal explanation of the study and a Parent Information and Consent Form will be provided. Where the parents of an eligible infant do not speak English sufficient to give informed consent, interpreters will be used to assist with the consent process.

The ÉCLAT study has received ethics approval from the Human Research Ethics Committees of The Royal Women's Hospital, Melbourne, Australia and Monash Health, Melbourne, Australia.

Patient and public involvement

Both human research and ethics committees at each recruitment centre have consumer input before trial approval to determine suitability of study design and consent forms.

Adverse events

Adverse events (AEs) are recorded within 7 days after the randomised extubation. They are recorded as part of the study design and secondary outcomes of ÉCLAT. The site investigators are responsible for recording all AEs regardless of their relationship to the intervention. The following outcome are designated as AEs:

- Necrotising enterocolitis (Bell's stage III or IV) (17)
- Intraventricular haemorrhage (grade III or IV)

Serious adverse events

Serious adverse events (SAEs) are recorded within 7 days after the randomised extubation. All are prespecified secondary outcomes of ÉCLAT. The investigators are responsible for recording all events regardless of their relationship to the intervention. All

SAE's are reported to an independent Data Safety Monitoring Committee (DSMC) and the local ethics committee within 72 hours of the principle investigator being notified. The following outcomes are designated as SAEs:

- Death
- Spontaneous intestinal perforation
- Pneumothorax
- Pulmonary interstitial emphysema

Study Oversight

The independent DMSC established for the ÉCLAT trial have their roles and responsibilities detailed in a separate DSMC Charter. The DSMC includes two independent, experienced neonatologists, and a senior statistician. The terms of reference for the DSMC include performance of interim safety analyses, periodic examination of relevant emerging external evidence, monitoring of adverse events, compliance with the trial protocol, and progress of recruitment. Safety analyses by the DMSC are planned after the primary outcome is known for the first 50 and 100 infants and will occur blinded to group allocation. If required, an additional safety analysis will be performed at 150 infants. No interim analyses of the primary outcome are planned.

Clinical Significance

Extubation failure is common in extremely preterm infants and associated with important neonatal morbidities (2). CPAP is the most commonly used form of non-invasive ventilation used post-extubation but the optimal pressure to use for this indication remains uncertain. The ÉCLAT study will reveal novel information regarding CPAP pressures in extremely preterm infants. The ÉCLAT study is the largest trial comparing and researching CPAP pressures >8 cm H_2O. Results from ÉCLAT will inform clinical practice and support clinicians in understanding and optimising CPAP pressures for extremely preterm infants. Results from this study will be disseminated via peer-reviewed journals and presented at national and international scientific conferences.

Author Statement

RB, AM and AK developed the concept and RB and AK wrote the protocol. BM, RAB, AM and PD gave input into the protocol and revised the manuscript. SD designed the statistical

analysis and revised the manuscript. All authors have read and approved the final manuscript and are accountable for its accuracy.

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Competing interests

None declared.

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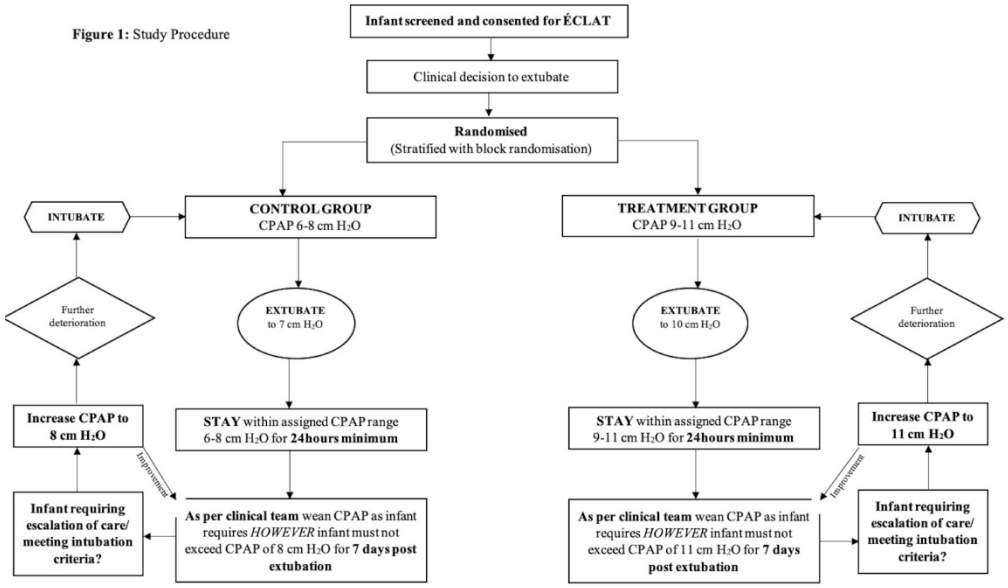
List of figures:

Figure 1: Study Procedure



ÉCLAT Study Procedure

146x90mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	10

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a no trial sponsor. investigator led trial
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a no trial sponsor. investigator led trial
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-10
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be	4

		collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a unblinded trial
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a unblinded trial
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a no long term follow up
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	4
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	4
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	4
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	2
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	1
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	9
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a no biological specimens

Notes:

- 5b: n/a no trial sponsor. investigator led trial
- 5c: n/a no trial sponsor. investigator led trial
- 17a: n/a unblinded trial
- 17b: n/a unblinded trial
- 18b: n/a no long term follow up
- 33: n/a no biological specimens This checklist was completed on 15. October 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

A randomised Controlled Trial Comparing Two CPAP Levels to Prevent Extubation failure in Extremely Preterm Infants.

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Title Page

Title:

A randomised Controlled Trial Comparing Two CPAP Levels to Prevent Extubation failure in Extremely Preterm Infants.

Authors

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Trial Registration

Australia and New Zealand Clinical Trial Registry: ACTRN12618001638224

Keywords:

Extremely preterm, infant, endotracheal extubation, continuous positive airway pressure.

Data sharing statement:

The protocol will be published and publicly available, and the de-identified individual patient datasets and statistical codes will be available on reasonable request.

Word count: 2604

Abstract

Introduction: Respiratory distress syndrome (RDS) is a complication of prematurity and extremely preterm infants born before 28 weeks' gestation often require endotracheal intubation and mechanical ventilation. In this high-risk population, mechanical ventilation is associated with lung injury and contributes to bronchopulmonary dysplasia. Therefore, clinicians attempt to extubate infants as quickly and use non-invasive respiratory support such as nasal continuous positive airway pressure (CPAP) to facilitate the transition. However, approximately 60% of extremely preterm infants experience 'extubation failure' and require re-intubation. Whilst CPAP pressures of 5-8cmH2O are commonly used, the optimal CPAP pressure is unknown, and higher pressures may be beneficial in avoiding extubation failure. Our trial is the Extubation CPAP Level Assessment Trial (ÉCLAT). The aim of this trial is to compare higher CPAP pressures 9-11cmH20 with a current standard pressures of 6-8cmH2O on extubation failure in extremely preterm infants.

Methods and analysis: 200 extremely preterm infants will be recruited prior to their first extubation from mechanical ventilation to CPAP. This is a parallel group randomised controlled trial. Infants will be randomised to one of two set CPAP pressures: CPAP10cmH2O (intervention) or CPAP 7cmH2O (control). The primary outcome will be extubation failure (re-intubation) within seven-days. Statistical analysis will follow standard methods for randomised trials on an intention to treat basis. For the primary outcome, this will be by intention to treat, adjusted for the pre-randomisation strata (GA and centre). We will use the appropriate parametric and non-parametric statistical tests.

Ethics and dissemination: Ethics approval has been granted by the Monash Health Human Research Ethics Committees. Amendments to the trial protocol will be submitted for approval. The findings of this study will be disseminated via peer-reviewed journals and presented at

national and international conferences. This trial was prospectively registered with Australia and New Zealand Clinical Trial Registry ACTRN12618001638224.

Article Summary

Strengths and limitations of this study:

- This study is a multicentre randomised controlled trial
- This study is the largest trial comparing CPAP pressure ranges to reduce extubation failure in extremely preterm infants
- CPAP pressures as high as 9-11cm H_2O are yet to be formally evaluated in extremely preterm infants
- Due to the nature of the interventions blinding of patients and clinicians are unable to occur.

Introduction

Respiratory distress syndrome (RDS) is common in preterm infants, and almost universal in extremely preterm infants born <28 weeks' gestation. In this high-risk population, bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, is a major morbidity following RDS and its treatment (1). Many extremely preterm infants require endotracheal intubation and mechanical ventilation (1). Mechanical ventilation, particularly if prolonged, injures the lungs and contributes to BPD (2). Consequently, avoiding or minimising the time that extremely preterm infants are mechanically ventilated is critical.

The optimal way to provide respiratory support to extremely preterm infants after mechanical ventilation remains under investigation, and the transition from mechanical ventilation to non-invasive respiratory support remains a poorly understood process (2). There is a paucity of data on the optimal timing of extubation, criteria for readiness for extubation, and the best strategy to use when providing post-extubation respiratory support (3). The extubation failure rate in extremely preterm infants is high (4), and reducing this outcome must be a focus of research.

Nasal continuous positive airway pressure (CPAP) is the most frequently used mode of non-invasive support used after extubation of extremely preterm infants. The reasons for extubation failure during CPAP are multifactorial. Variables such as infant weight (birth weight <750g), immaturity (<26 weeks' gestation) and the severity of RDS (alveolar-arterial gradient >180 mm Hg) are weakly predictive of early CPAP failure in very preterm infants (5). The use of a set CPAP pressure sufficient to maintain functional residual capacity is likely to be

important (6). The optimal CPAP pressure to use after extubation is unknown, although a meta-analysis of studies suggests that pressures of at least 5 cm H_2O are needed (6). Many infants are re-intubated following extubation for increased oxygen requirement and work of breathing suggesting that a low end-expiratory lung volume may contribute to extubation failure (5).

Utilising higher CPAP pressures post-extubation may prevent alveolar collapse, improve lung function and reduce extubation failure (7,8). Kitsommart *et al* compared CPAP 7-9 cm H_2O with CPAP 4-6 cm H_2O after extubation of infants with birth weight <1250 g and demonstrated no difference in extubation failure within 72 hours (7). In a second trial, Buzzella *et al* randomised very preterm infants born 23-30 weeks' gestation with RDS to receive either CPAP 7-9 cm H_2O or CPAP 4-6 cm H_2O after extubation (8). Rates of extubation failure within 96 hours were significantly lower in the group randomised to the higher range of CPAP pressures (8). Current CPAP pressure recommendations are wide and varied (6). Most clinicians report pressures of 5-8 cm H_2O however, use of CPAP pressures up to 12 cm H_2O have been reported and have not been associated with adverse effects (9).

In extremely preterm infants, extubation failure is associated with significant morbidities, including BPD, pulmonary vascular disease, airway trauma, poor feeding and oral aversion, adverse neurodevelopmental outcomes, and delayed family unit bonding (10). Thus, improving rates of successful extubation in this high-risk population of preterm infants is a clinical priority (10–14). The ÈCLAT trial will investigate the CPAP pressure range of 6-8 cm H_2O, routinely used in our clinical practice, with a higher-pressure range of 9-11 cm H_2O. We hypothesise that the higher-pressure range will result in less atelectatic pulmonary failure and extubation failure.

Methods and analysis

Study design and aim

We used the SPIRIT checklist when writing our report (15). This is a multicentre, unblinded, randomised controlled trial. The aim of the ÉCLAT study is to determine, in extremely preterm infants born <28 weeks' gestation who are undergoing their first extubation, whether extubation to a higher CPAP pressure (10 cm H_2O, range 9-11 cm H_2O), compared with a standard CPAP pressure (7 cm H_2O, range 6-8 cm H_2O) decreases extubation failure within seven days.

Sample size

The rates of extubation failure within 7 days in extremely preterm infants at the participating centres is estimated at 55%. To detect a reduction in extubation failure from 55% to 35% (absolute risk reduction 20%, relative risk reduction 40%) with 80% power and a two-tailed alpha error of 0.05, a sample size of 93 infants in each arm (total 186 infants) is required.

Patient population

Infants born extremely preterm (<28 weeks' gestation) who are intubated and mechanically ventilated and being extubated for the first time are eligible for participation in the ÉCLAT trial. The timing of the extubation is determined by the clinical team caring for the infant, and there is no postnatal age limit for participation.

Inclusion criteria

Infants are eligible if they:

- were born <28 completed weeks' gestation
- are being extubated for the first time from mechanical ventilation to nasal CPAP
- have received enteral or intravenous caffeine (as prophylaxis for apnoea of prematurity) <24 hours prior to the planned extubation
- have received exogenous surfactant treatment.

Exclusion criteria

Infants are excluded if they:

- are being extubated to any other mode of non-invasive respiratory support other than nasal CPAP, or to no respiratory support
- have a major congenital anomaly or condition that might adversely affect breathing or ventilation: e.g. known upper airway obstruction or major airway abnormality, or major congenital heart disease
- are not receiving full intensive care after extubation.

Randomisation

Enrolled infants are randomised using REDCap electronic data capture tools (16), hosted at the Murdoch Children's Research Institute, Melbourne, Australia. REDCap (Research Electronic Data Capture) is a secure, password encrypted, web-based application designed to support data capture and randomisation for research studies. Only the infant's first extubation is randomised. Multiple births are randomised individually. Randomisation occurs

after the clinical decision to extubate has been made and shortly before extubation using a computer or smartphone. Stratification is by centre and gestational age at birth (<26 weeks; ≥26 weeks).

Clinical Management [Figure one]

Higher CPAP pressure (Intervention)

Infants are extubated to a set CPAP pressure of **10 cm H_2O**. Whilst receiving CPAP, infants will remain within a set CPAP pressure range of **9 cm H_2O – 11 cm H_2O** for at least **24 hours,** with changes within this range at the discretion of the treating team. After 24 hours, infants may have their set CPAP pressure weaned at the discretion of the treating team but must remain within a set CPAP pressure range **5 cm H_2O – 11 cm H_2O** for at least **7 days** after extubation if receiving CPAP. Infants are re-intubated if they satisfy the extubation failure criteria described below within 7 days after extubation. The fraction of inspired oxygen (FiO_2) is titrated to keep oxygen saturations (SpO_2) in the standard target ranges of the participating unit. If extubation failure occurs, management following re-intubation will be at the discretion of the treating team. For subsequent extubations, clinicians will be encouraged to use the assigned set CPAP pressure range (see figure one).

Standard CPAP pressure (control)

Infants are extubated to a set CPAP pressure of **7 cm H_2O**. Whilst receiving CPAP, infants will remain within a set CPAP pressure range of **6 cm H_2O – 8 cm H_2O** for at least **24 hours,** with changes to the set CPAP pressure within this range at the discretion of the treating team. After 24 hours, infants may have their set CPAP pressure weaned at the discretion of the treating team but must remain within a set CPAP pressure range **5 cm H_2O – 8 cm H_2O** for at least **7 days** after extubation if receiving CPAP. Infants are re-intubated if they satisfy the extubation failure criteria described below within 7 days after extubation. The FiO_2 is titrated to keep SpO_2 in the standard target ranges of the participating unit. If extubation failure occurs, management following re-intubation will be at the discretion of the treating team. For subsequent extubations, clinicians will be encouraged to use the assigned set CPAP pressure range (see figure one).

Device

In both groups, infants will be extubated to continuous-flow nasal CPAP, via a mechanical ventilator (either the Dräger VN500, Dräger Medical, Lübeck, Germany, or the SLE 5000, SLE, Croydon, UK) operating in CPAP mode. After 24 hours the infant may be transitioned to 'bubble' nasal CPAP (Fisher & Paykel bubble CPAP circuit, Fisher & Paykel Healthcare, Auckland, New Zealand) but only if receiving a CPAP ≤ 10cmH_2O given the pressure limitations of the 'bubble' CPAP device. Nasal CPAP may be delivered via any binasal CPAP prongs or mask, according to the participating unit's protocol. Nasal prongs should be sized as per the manufactures guidelines to the largest size to occlude the infant's nares.

Outcomes

Extubation Failure

The primary outcome is extubation failure within 7 days, defined as receiving the *maximum* CPAP level (11 cm H_2O in the intervention group; 8 cm H_2O in the control group) and having at least one of:

- FiO_2 requirement >0.20 above the pre-extubation FiO_2
- Two or more apnoeic episodes within any 24-hour period requiring intermittent positive pressure ventilation, or six or more apnoeic events requiring stimulation in any 6-hour period
- Respiratory acidosis with pH <7.2 *and* pCO_2 >60 mm Hg
- Require urgent intubation for an acute deterioration (at clinical discretion) with the reason for re-intubation documented.

Treatment failure

Should infants not be immediately reintubated and instead managed with non-invasive positive pressure ventilation or escalated to a higher CPAP pressure than their assigned range they will be documented as an extubation failure and reported as a protocol violation.

Secondary outcomes

- Incidence of re-intubation within 72 hours, and within 96 hours
- Failure in hours after extubation
    - Reason(s) for extubation failure
    - Kaplan Meier Survival curve between both groups
- Death before hospital discharge

- Duration of mechanical ventilation in days after randomisation in survivors
- Total duration of hospitalisation in days in survivors
- Postmenstrual age at last supplemental oxygen, and at last positive pressure ventilation (mechanical ventilation, CPAP [or variants], or nasal high-flow >2 Litres per minute) in survivors
- Incidence of treatment with systemic postnatal corticosteroids for lung disease after randomisation
- Incidence of new pneumothorax requiring drainage with thoracocentesis or intercostal catheter insertion after randomisation
- Incidence of new, radiologically-diagnosed pulmonary interstitial emphysema after randomisation
- Incidence of BPD, defined as a requirement for supplemental oxygen and/or respiratory support (mechanical ventilation, CPAP [or variants], or nasal high-flow >2 Litres per minute) at 36 weeks' post-menstrual age
- Incidence of necrotising enterocolitis Bell's stage 2 or above after randomisation (17)
- Incidence of spontaneous intestinal perforation after randomisation
- Incidence of retinopathy of prematurity requiring treatment with laser therapy or intra-ocular medication in one or both eyes after randomisation
- Incidence of new diagnosis of grade 3 or 4 intraventricular haemorrhage after randomisation

Other data

Data collected will include:

- Maternal and infant demographics: maternal parity, infant sex, gestational age at birth, birth weight in grams, mode of delivery, exposure to any antenatal corticosteroids, duration of ruptured membranes prior to delivery in days, presence of histologically diagnosed chorioamnionitis
- Postnatal age at extubation in days, last weight prior to extubation in grams, age at first intubation in hours
- Previous dose of exogenous surfactant received in milligrams/kilogram, prior treatment for a patent ductus arteriosus (pharmacological or surgical), prior systemic postnatal corticosteroids for lung disease

- Mechanical ventilator settings immediately prior to extubation (mode, mean airway pressure in mmHg, FiO_2, tidal volumes (set and achieved), peak pressures (set and achieved) and end expiratory pressure.
- Blood gas analysis results within 24 hours prior to extubation (if applicable): lowest pH, highest pCO_2, lowest base excess.

Data analysis plan

Statistical analysis will follow standard methods for randomised trials. For the primary outcome, the analysis will be by intention to treat and be adjusted for the pre-randomisation strata (GA and centre). For dichotomous outcomes, including the primary outcome, the two treatment groups will be compared using risk difference with 95% CI, both overall, and within the pre-specified subgroups (gestational age at birth <26 weeks, ≥26 weeks). For dichotomous secondary outcomes, analysis will be limited to the two treatment groups, using risk difference with 95% CI. For continuous outcomes, the two treatment groups will be compared using difference of means, together with 95% CI, for outcome variables which are normally distributed; for outcome variables, which are not normally distributed, the comparison will be difference of medians, with 95% CI. All comparisons (risk difference, difference of means, difference of medians) will be estimated using regression models with the randomisation strata as covariates, and with standard errors adjusted to take into account the clustering due to multiple births. Reporting of findings will be done in accordance with CONSORT guidelines.

Ethics and Dissemination

Infants are only enrolled after prospective, informed, written parental consent. Parent(s) of eligible infants will be approached by a member of the research team. A verbal explanation of the study and a Parent Information and Consent Form will be provided. Where the parents of an eligible infant do not speak English sufficient to give informed consent, interpreters will be used to assist with the consent process.

The ÉCLAT study has received ethics approval from the Human Research Ethics Committees of The Royal Women's Hospital, Melbourne, Australia and Monash Health, Melbourne, Australia.

Patient and public involvement

Both human research and ethics committees at each recruitment centre have consumer input before trial approval to determine suitability of study design and consent forms.

Adverse events

Adverse events (AEs) are recorded within 7 days after the randomised extubation. They are recorded as part of the study design and secondary outcomes of ÉCLAT. The site investigators are responsible for recording all AEs regardless of their relationship to the intervention. The following outcome are designated as AEs:

- Necrotising enterocolitis (Bell's stage III or IV) (17)
- Intraventricular haemorrhage (grade III or IV)

Serious adverse events

Serious adverse events (SAEs) are recorded within 7 days after the randomised extubation. All are prespecified secondary outcomes of ÉCLAT. The investigators are responsible for recording all events regardless of their relationship to the intervention. All SAE's are reported to an independent Data Safety Monitoring Committee (DSMC) and the local ethics committee within 72 hours of the principle investigator being notified. The following outcomes are designated as SAEs:

- Death
- Spontaneous intestinal perforation
- Pneumothorax
- Pulmonary interstitial emphysema

Study Oversight

The independent DMSC established for the ÉCLAT trial have their roles and responsibilities detailed in a separate DSMC Charter. The DSMC includes two independent, experienced neonatologists, and a senior statistician. The terms of reference for the DSMC include performance of interim safety analyses, periodic examination of relevant emerging external evidence, monitoring of adverse events, compliance with the trial protocol, and progress of recruitment. Safety analyses by the DMSC are planned after the primary outcome is known for the first 50 and 100 infants and will occur blinded to group allocation. If required, an additional safety analysis will be performed at 150 infants. No interim analyses of the primary outcome are planned.

Clinical Significance

Extubation failure is common in extremely preterm infants and associated with important neonatal morbidities (18). CPAP is the most commonly used form of non-invasive ventilation used post-extubation but the optimal pressure to use for this indication remains uncertain. The ÉCLAT study will reveal novel information regarding CPAP pressures in extremely preterm infants. The ÉCLAT study is the largest trial comparing and researching CPAP pressures >8 cm H_2O. Results from ÉCLAT will inform clinical practice and support clinicians in understanding and optimising CPAP pressures for extremely preterm infants. Results from this study will be disseminated via peer-reviewed journals and presented at national and international scientific conferences.

Author Statement

RB, AM and AK developed the concept and RB and AK wrote the protocol. BM, RAB, AM and PD gave input into the protocol and revised the manuscript. SD designed the statistical analysis and revised the manuscript. All authors have read and approved the final manuscript and are accountable for its accuracy.

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Competing interests

None declared.

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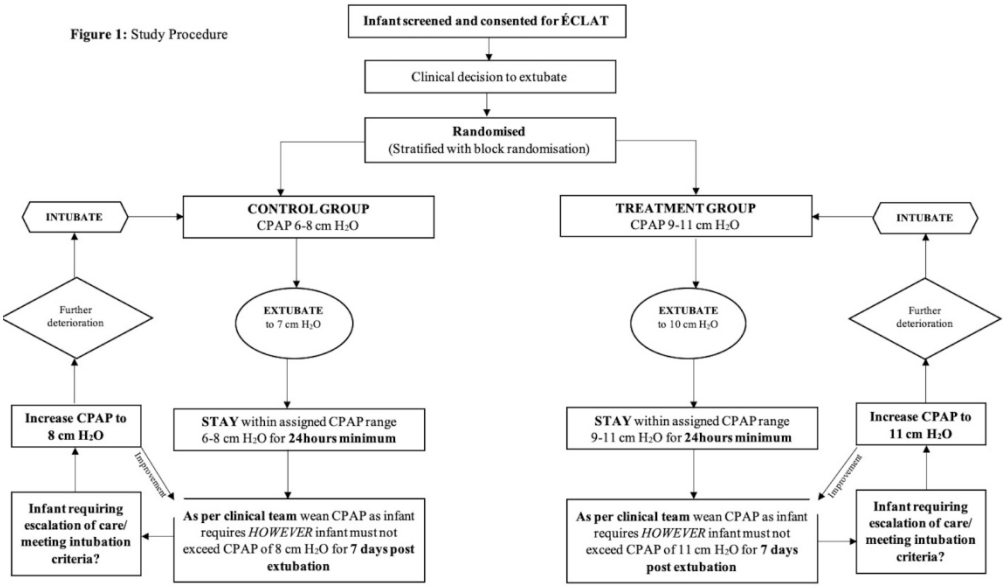
List of figures:

Figure 1: Study Procedure

Supplemental file 1:

Model Participant Information and Consent Form



ÉCLAT Study Procedure

146x90mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	11
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	1,10,11

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4,5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8,9

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	5

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A no long term follow-up
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	4
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	4
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	4
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	10

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7,8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	2
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	15
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Notes:

- 18b: N/A no long term follow-up This checklist was completed on 03. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Protocol for a Randomised Controlled Trial Comparing Two CPAP Levels to Prevent Extubation failure in Extremely Preterm Infants

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Title Page

Title:

Protocol for a Randomised Controlled Trial Comparing Two CPAP Levels to Prevent Extubation failure in Extremely Preterm Infants.

Authors

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Trial Registration

Australia and New Zealand Clinical Trial Registry: ACTRN12618001638224

Keywords:

Extremely preterm, infant, endotracheal extubation, continuous positive airway pressure.

Data sharing statement:

The protocol will be published and publicly available, and the de-identified individual patient datasets and statistical codes will be available on reasonable request.

Word count: 2604

Abstract

Introduction: Respiratory distress syndrome (RDS) is a complication of prematurity and extremely preterm infants born before 28 weeks' gestation often require endotracheal intubation and mechanical ventilation. In this high-risk population, mechanical ventilation is associated with lung injury and contributes to bronchopulmonary dysplasia. Therefore, clinicians attempt to extubate infants as quickly and use non-invasive respiratory support such as nasal continuous positive airway pressure (CPAP) to facilitate the transition. However, approximately 60% of extremely preterm infants experience 'extubation failure' and require re-intubation. Whilst CPAP pressures of 5-8cmH2O are commonly used, the optimal CPAP pressure is unknown, and higher pressures may be beneficial in avoiding extubation failure. Our trial is the Extubation CPAP Level Assessment Trial (ÉCLAT). The aim of this trial is to compare higher CPAP pressures 9-11cmH20 with a current standard pressures of 6-8cmH2O on extubation failure in extremely preterm infants.

Methods and analysis: 200 extremely preterm infants will be recruited prior to their first extubation from mechanical ventilation to CPAP. This is a parallel group randomised controlled trial. Infants will be randomised to one of two set CPAP pressures: CPAP10cmH2O (intervention) or CPAP 7cmH2O (control). The primary outcome will be extubation failure (re-intubation) within seven-days. Statistical analysis will follow standard methods for randomised trials on an intention to treat basis. For the primary outcome, this will be by intention to treat, adjusted for the pre-randomisation strata (GA and centre). We will use the appropriate parametric and non-parametric statistical tests.

Ethics and dissemination: Ethics approval has been granted by the Monash Health Human Research Ethics Committees. Amendments to the trial protocol will be submitted for approval. The findings of this study will be written into a clinical trial report manuscript and disseminated

via peer-reviewed journals (on-line or in press) and presented at national and international conferences. This trial was prospectively registered with Australia and New Zealand Clinical Trial Registry ACTRN12618001638224.

Article Summary

Strengths and limitations of this study:

- This study is a multicentre randomised controlled trial
- This study is the largest trial comparing CPAP pressure ranges to reduce extubation failure in extremely preterm infants
- CPAP pressures as high as 9-11cm H_2O are yet to be formally evaluated in extremely preterm infants
- Due to the nature of the interventions blinding of patients and clinicians are unable to occur.

Introduction

Respiratory distress syndrome (RDS) is common in preterm infants, and almost universal in extremely preterm infants born <28 weeks' gestation. In this high-risk population, bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, is a major morbidity following RDS and its treatment (1). Many extremely preterm infants require endotracheal intubation and mechanical ventilation (1). Mechanical ventilation, particularly if prolonged, injures the lungs and contributes to BPD (2). Consequently, avoiding or minimising the time that extremely preterm infants are mechanically ventilated is critical.

The optimal way to provide respiratory support to extremely preterm infants after mechanical ventilation remains under investigation, and the transition from mechanical ventilation to non-invasive respiratory support remains a poorly understood process (2). There is a paucity of data on the optimal timing of extubation, criteria for readiness for extubation, and the best strategy to use when providing post-extubation respiratory support (3). The extubation failure rate in extremely preterm infants is high (4), and reducing this outcome must be a focus of research.

Nasal continuous positive airway pressure (CPAP) is the most frequently used mode of non-invasive support used after extubation of extremely preterm infants. The reasons for extubation failure during CPAP are multifactorial. Variables such as infant weight (birth weight <750g), immaturity (<26 weeks' gestation) and the severity of RDS (alveolar-arterial gradient >180 mm Hg) are weakly predictive of early CPAP failure in very preterm infants (5). The use

of a set CPAP pressure sufficient to maintain functional residual capacity is likely to be important (6). The optimal CPAP pressure to use after extubation is unknown, although a meta-analysis of studies suggests that pressures of at least 5 cm H_2O are needed (6). Many infants are re-intubated following extubation for increased oxygen requirement and work of breathing suggesting that a low end-expiratory lung volume may contribute to extubation failure (5).

Utilising higher CPAP pressures post-extubation may prevent alveolar collapse, improve lung function and reduce extubation failure (7,8). Kitsommart *et al* compared CPAP 7-9 cm H_2O with CPAP 4-6 cm H_2O after extubation of infants with birth weight <1250 g and demonstrated no difference in extubation failure within 72 hours (7). In a second trial, Buzzella *et al* randomised very preterm infants born 23-30 weeks' gestation with RDS to receive either CPAP 7-9 cm H_2O or CPAP 4-6 cm H_2O after extubation (8). Rates of extubation failure within 96 hours were significantly lower in the group randomised to the higher range of CPAP pressures (8). Current CPAP pressure recommendations are wide and varied (6). Most clinicians report pressures of 5-8 cm H_2O however, use of CPAP pressures up to 12 cm H_2O have been reported and have not been associated with adverse effects (9).

In extremely preterm infants, extubation failure is associated with significant morbidities, including BPD, pulmonary vascular disease, airway trauma, poor feeding and oral aversion, adverse neurodevelopmental outcomes, and delayed family unit bonding (10). Thus, improving rates of successful extubation in this high-risk population of preterm infants is a clinical priority (10–14). The ÈCLAT trial will investigate the CPAP pressure range of 6-8 cm H_2O, routinely used in our clinical practice, with a higher-pressure range of 9-11 cm H_2O. We hypothesise that the higher-pressure range will result in less atelectatic pulmonary failure and extubation failure.

Methods and analysis

Study design and aim

We used the SPIRIT checklist when writing our report (15). This is a multicentre, unblinded, randomised controlled trial. The aim of the ÉCLAT study is to determine, in extremely preterm infants born <28 weeks' gestation who are undergoing their first extubation, whether extubation to a higher CPAP pressure (10 cm H_2O, range 9-11 cm H_2O), compared with a standard CPAP pressure (7 cm H_2O, range 6-8 cm H_2O) decreases extubation failure within seven days.

Sample size

The rates of extubation failure within 7 days in extremely preterm infants at the participating centres is estimated at 55%. To detect a reduction in extubation failure from 55% to 35% (absolute risk reduction 20%, relative risk reduction 40%) with 80% power and a two-tailed alpha error of 0.05, a sample size of 93 infants in each arm (total 186 infants) is required.

Patient population

Infants born extremely preterm (<28 weeks' gestation) who are intubated and mechanically ventilated and being extubated for the first time are eligible for participation in the ÉCLAT trial. The timing of the extubation is determined by the clinical team caring for the infant, and there is no postnatal age limit for participation.

Inclusion criteria

Infants are eligible if they:

- were born <28 completed weeks' gestation
- are being extubated for the first time from mechanical ventilation to nasal CPAP
- have received enteral or intravenous caffeine (as prophylaxis for apnoea of prematurity) <24 hours prior to the planned extubation
- have received exogenous surfactant treatment.

Exclusion criteria

Infants are excluded if they:

- are being extubated to any other mode of non-invasive respiratory support other than nasal CPAP, or to no respiratory support
- have a major congenital anomaly or condition that might adversely affect breathing or ventilation: e.g. known upper airway obstruction or major airway abnormality, or major congenital heart disease
- are not receiving full intensive care after extubation.

Randomisation

Enrolled infants are randomised using REDCap electronic data capture tools (16), hosted at the Murdoch Children's Research Institute, Melbourne, Australia. REDCap (Research Electronic Data Capture) is a secure, password encrypted, web-based application designed to support data capture and randomisation for research studies. Only the infant's first extubation is randomised. Multiple births are randomised individually. Randomisation occurs

after the clinical decision to extubate has been made and shortly before extubation using a computer or smartphone. Stratification is by centre and gestational age at birth (<26 weeks; ≥26 weeks).

Clinical Management [Figure one]

Higher CPAP pressure (Intervention)

Infants are extubated to a set CPAP pressure of **10 cm H_2O**. Whilst receiving CPAP, infants will remain within a set CPAP pressure range of **9 cm H_2O – 11 cm H_2O** for at least **24 hours,** with changes within this range at the discretion of the treating team. After 24 hours, infants may have their set CPAP pressure weaned at the discretion of the treating team but must remain within a set CPAP pressure range **5 cm H_2O – 11 cm H_2O** for at least **7 days** after extubation if receiving CPAP. Infants are re-intubated if they satisfy the extubation failure criteria described below within 7 days after extubation. The fraction of inspired oxygen (FiO_2) is titrated to keep oxygen saturations (SpO_2) in the standard target ranges of the participating unit. If extubation failure occurs, management following re-intubation will be at the discretion of the treating team. For subsequent extubations, clinicians will be encouraged to use the assigned set CPAP pressure range (see figure one).

Standard CPAP pressure (control)

Infants are extubated to a set CPAP pressure of **7 cm H_2O**. Whilst receiving CPAP, infants will remain within a set CPAP pressure range of **6 cm H_2O – 8 cm H_2O** for at least **24 hours,** with changes to the set CPAP pressure within this range at the discretion of the treating team. After 24 hours, infants may have their set CPAP pressure weaned at the discretion of the treating team but must remain within a set CPAP pressure range **5 cm H_2O – 8 cm H_2O** for at least **7 days** after extubation if receiving CPAP. Infants are re-intubated if they satisfy the extubation failure criteria described below within 7 days after extubation. The FiO_2 is titrated to keep SpO_2 in the standard target ranges of the participating unit. If extubation failure occurs, management following re-intubation will be at the discretion of the treating team. For subsequent extubations, clinicians will be encouraged to use the assigned set CPAP pressure range (see figure one).

Device

In both groups, infants will be extubated to continuous-flow nasal CPAP, via a mechanical ventilator (either the Dräger VN500, Dräger Medical, Lübeck, Germany, or the SLE 5000, SLE, Croydon, UK) operating in CPAP mode. After 24 hours the infant may be transitioned to 'bubble' nasal CPAP (Fisher & Paykel bubble CPAP circuit, Fisher & Paykel Healthcare, Auckland, New Zealand) but only if receiving a CPAP ≤ 10cmH_2O given the pressure limitations of the 'bubble' CPAP device. Nasal CPAP may be delivered via any binasal CPAP prongs or mask, according to the participating unit's protocol. Nasal prongs should be sized as per the manufactures guidelines to the largest size to occlude the infant's nares.

Outcomes

Extubation Failure

The primary outcome is extubation failure within 7 days, defined as receiving the *maximum* CPAP level (11 cm H_2O in the intervention group; 8 cm H_2O in the control group) and having at least one of:

- FiO_2 requirement >0.20 above the pre-extubation FiO_2
- Two or more apnoeic episodes within any 24-hour period requiring intermittent positive pressure ventilation, or six or more apnoeic events requiring stimulation in any 6-hour period
- Respiratory acidosis with pH <7.2 *and* pCO_2 >60 mm Hg
- Require urgent intubation for an acute deterioration (at clinical discretion) with the reason for re-intubation documented.

Treatment failure

Should infants not be immediately reintubated and instead managed with non-invasive positive pressure ventilation or escalated to a higher CPAP pressure than their assigned range they will be documented as an extubation failure and reported as a protocol violation.

Secondary outcomes

- Incidence of re-intubation within 72 hours, and within 96 hours
- Failure in hours after extubation
    - Reason(s) for extubation failure
    - Kaplan Meier Survival curve between both groups
- Death before hospital discharge

- Duration of mechanical ventilation in days after randomisation in survivors
- Total duration of hospitalisation in days in survivors
- Postmenstrual age at last supplemental oxygen, and at last positive pressure ventilation (mechanical ventilation, CPAP [or variants], or nasal high-flow >2 Litres per minute) in survivors
- Incidence of treatment with systemic postnatal corticosteroids for lung disease after randomisation
- Incidence of new pneumothorax requiring drainage with thoracocentesis or intercostal catheter insertion after randomisation
- Incidence of new, radiologically-diagnosed pulmonary interstitial emphysema after randomisation
- Incidence of BPD, defined as a requirement for supplemental oxygen and/or respiratory support (mechanical ventilation, CPAP [or variants], or nasal high-flow >2 Litres per minute) at 36 weeks' post-menstrual age
- Incidence of necrotising enterocolitis Bell's stage 2 or above after randomisation (17)
- Incidence of spontaneous intestinal perforation after randomisation
- Incidence of retinopathy of prematurity requiring treatment with laser therapy or intra-ocular medication in one or both eyes after randomisation
- Incidence of new diagnosis of grade 3 or 4 intraventricular haemorrhage after randomisation

Other data

Data collected will include:

- Maternal and infant demographics: maternal parity, infant sex, gestational age at birth, birth weight in grams, mode of delivery, exposure to any antenatal corticosteroids, duration of ruptured membranes prior to delivery in days, presence of histologically diagnosed chorioamnionitis
- Postnatal age at extubation in days, last weight prior to extubation in grams, age at first intubation in hours
- Previous dose of exogenous surfactant received in milligrams/kilogram, prior treatment for a patent ductus arteriosus (pharmacological or surgical), prior systemic postnatal corticosteroids for lung disease

- Mechanical ventilator settings immediately prior to extubation (mode, mean airway pressure in mmHg, FiO_2, tidal volumes (set and achieved), peak pressures (set and achieved) and end expiratory pressure.
- Blood gas analysis results within 24 hours prior to extubation (if applicable): lowest pH, highest pCO_2, lowest base excess.

Data analysis plan

Statistical analysis will follow standard methods for randomised trials. For the primary outcome, the analysis will be by intention to treat and be adjusted for the pre-randomisation strata (GA and centre). For dichotomous outcomes, including the primary outcome, the two treatment groups will be compared using risk difference with 95% CI, both overall, and within the pre-specified subgroups (gestational age at birth <26 weeks, ≥26 weeks). For dichotomous secondary outcomes, analysis will be limited to the two treatment groups, using risk difference with 95% CI. For continuous outcomes, the two treatment groups will be compared using difference of means, together with 95% CI, for outcome variables which are normally distributed; for outcome variables, which are not normally distributed, the comparison will be difference of medians, with 95% CI. All comparisons (risk difference, difference of means, difference of medians) will be estimated using regression models with the randomisation strata as covariates, and with standard errors adjusted to take into account the clustering due to multiple births. Reporting of findings will be done in accordance with CONSORT guidelines.

Ethics and Dissemination

Infants are only enrolled after prospective, informed, written parental consent (see supplementary file). Parent(s) of eligible infants will be approached by a member of the research team. A verbal explanation of the study and a Parent Information and Consent Form will be provided. Where the parents of an eligible infant do not speak English sufficient to give informed consent, interpreters will be used to assist with the consent process.

The ÉCLAT study has received ethics approval from the Human Research Ethics Committees of The Royal Women's Hospital, Melbourne, Australia and Monash Health, Melbourne, Australia.

Patient and public involvement

Both human research and ethics committees at each recruitment centre have consumer input before trial approval to determine suitability of study design and consent forms. Consumer input was in the form of a consumer advocate, this is a panel of non-clinical public who have had previous involvement in a neonatal intensive care setting for example, a previous parent.

Adverse events

Adverse events (AEs) are recorded within 7 days after the randomised extubation. They are recorded as part of the study design and secondary outcomes of ÉCLAT. The site investigators are responsible for recording all AEs regardless of their relationship to the intervention. The following outcome are designated as AEs:

- Necrotising enterocolitis (Bell's stage III or IV) (17)
- Intraventricular haemorrhage (grade III or IV)

Serious adverse events

Serious adverse events (SAEs) are recorded within 7 days after the randomised extubation. All are prespecified secondary outcomes of ÉCLAT. The investigators are responsible for recording all events regardless of their relationship to the intervention. All SAE's are reported to an independent Data Safety Monitoring Committee (DSMC) and the local ethics committee within 72 hours of the principle investigator being notified. The following outcomes are designated as SAEs:

- Death
- Spontaneous intestinal perforation
- Pneumothorax
- Pulmonary interstitial emphysema

Study Oversight

The independent DMSC established for the ÉCLAT trial have their roles and responsibilities detailed in a separate DSMC Charter. The DSMC includes two independent, experienced neonatologists, and a senior statistician. The terms of reference for the DSMC include performance of interim safety analyses, periodic examination of relevant emerging external evidence, monitoring of adverse events, compliance with the trial protocol, and progress of recruitment. Safety analyses by the DMSC are planned after the primary outcome is known for the first 50 and 100 infants and will occur blinded to group allocation. If required,

an additional safety analysis will be performed at 150 infants. No interim analyses of the primary outcome are planned.

Clinical Significance

Extubation failure is common in extremely preterm infants and associated with important neonatal morbidities (18). CPAP is the most commonly used form of non-invasive ventilation used post-extubation but the optimal pressure to use for this indication remains uncertain. The ÉCLAT study will reveal novel information regarding CPAP pressures in extremely preterm infants. The ÉCLAT study is the largest trial comparing and researching CPAP pressures >8 cm H_2O. Results from ÉCLAT will inform clinical practice and support clinicians in understanding and optimising CPAP pressures for extremely preterm infants. Results from this study will be disseminated via peer-reviewed journals and presented at national and international scientific conferences.

Author Statement

RB, AM and AK developed the concept and RB and AK wrote the protocol. BM, RAB, AM and PD gave input into the protocol and revised the manuscript. SD designed the statistical analysis and revised the manuscript. All authors have read and approved the final manuscript and are accountable for its accuracy.

Funding

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Competing interests

None declared.

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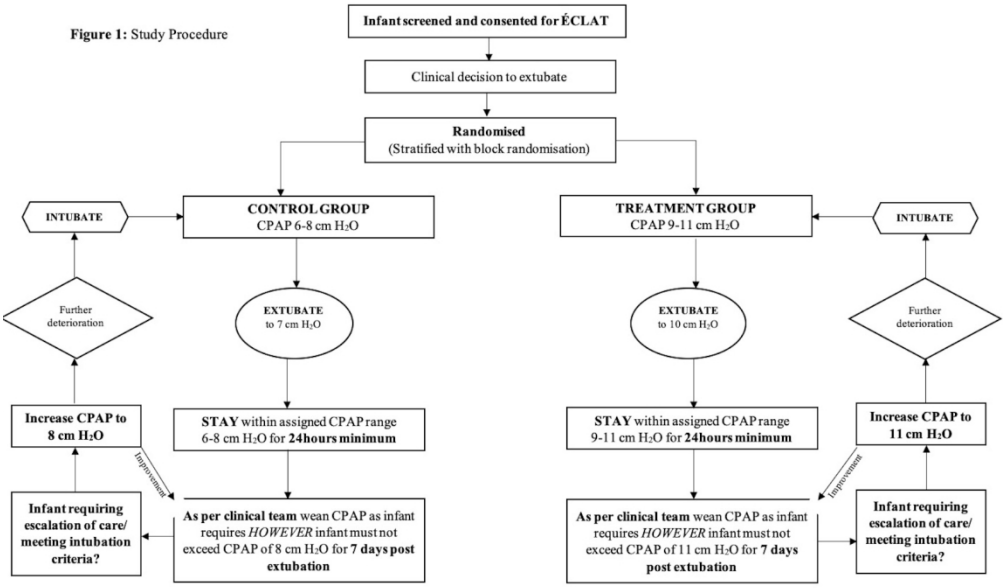
List of figures:

Figure 1: Study Procedure

Supplemental file 1:

Model Participant Information and Consent Form



ÉCLAT Study Procedure

146x90mm (300 x 300 DPI)

Master Participant Information Sheet/Consent Form – Parent/Guardian
Interventional Study - *Parent/Guardian consenting on behalf of participant*

Title	*Extubation CPAP Level Assessment Trial*
Short Title	*ÉCLAT*
Protocol Number	*1*
Project Sponsor	*Anna Kidman – PhD study*
Coordinating Principal Investigator/ Principal Investigator	*Anna Kidman & Dr Risha Bhatia (Monash Health)*
Associate Investigator(s)	*Dr Brett Manley (Royal Women's Hospital)* *Dr Rose Boland (Royal Women's Hospital)* *Professor Peter Davis (Royal Women's Hospital)*
Location	*Monash Newborn & Royal Women's Hospital*

Part 1 What does your baby's participation involve?

1. Introduction

This is an invitation for your baby in your care to take part in this research project because they are currently intubated with an endotracheal tube. The research project is testing the use of different air pressures on an existing type of respiratory support *Continuous Positive Airway Pressure* (CPAP) after the endotracheal tube is removed.

This Participant Information Sheet/Consent Form informs you of the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want your baby to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not your baby can take part, you might want to talk about it with a relative or friend.

Participation in this research is voluntary. If you do not wish your baby to take part, they do not have to. your baby will still receive the best possible care whether or not they take part. They will still receive the same CPAP care as those babies in the trial. The only difference will be your baby's data will not be recorded and used to further develop the extubation process.

If you decide you want your baby to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to your baby taking part in the research project
• Consent for your baby to have the tests and treatments that are described
• Consent to the use of your baby's personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research?

Your premature baby is currently intubated with an endotracheal tube to help them breath because they are requiring extra support. Soon the treating team will want to remove this tube to let your baby breathe on his/her own (extubate). Most often extremely premature infants will still require a form of *non-invasive* breathing support after the tube is removed to help hold their lungs open for a period of time.

Neonatal intensive care units are currently using Continuous Positive Airway Pressure (CPAP) as this support. CPAP involves short soft prongs that sit in your baby's nose connected to a circuit that delivers a continuous amount of distending pressure (and or oxygen) into your baby's lungs. This amount of pressure is measured in cm H_2O and can range from 4-12.

At the moment most babies, once extubated are prescribed a level of 7 cm H_2O. Sometimes a baby is not ready to have the breathing tube removed and so needs to be re-intubated.
The aim of our study is to compare the current practice of 7 cm H_2O to using higher pressures of 10 cm H_2O and to investigate whether the higher pressures of CPAP reduce re-intubation.

The results of this research will be used by Miss Anna Kidman to obtain a *Doctor of Philosophy* degree at the University of Melbourne.

3. What does participation in this research involve?

Your baby's participation in this study will involve the signing of witnessed, informed consent after he/she is screened for eligibility prior to him/her having their breathing tube removed.

When the doctors decide your baby is ready to try breathing by themselves, participation in the ÉCLAT study will involve your baby receiving a CPAP of 7 cm H_2O or 10 cm H_2O after his/her breathing tube is removed. Your baby will be participating in a randomised controlled research project. You will not be able to choose which CPAP level your baby will receive. To determine which level results in the better outcomes we need to compare different treatments. We put babies into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each baby is put into a group by chance (random).

Regardless of which group your baby is allocated to, they will continue to receive routine care from the doctors and nurses as they would without this trial. They will only have specific guidelines for how their breathing support will be managed.

If you choose to allow your baby to participate in the ÉCLAT study, they should not require any extra blood tests, procedures or investigations. There may be extra observations documented by medical and nursing staff however this will not disturb your baby in any way. If your baby has a change in condition the medical staff will escalate care appropriately regardless of what CPAP treatment your baby is receiving.

Your baby will remain in the study until discharge. Data will be collected from your baby's medical chart and there will be no follow up required after you are discharged from hospital.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids investigators or participants jumping to conclusions. There are no additional costs associated with participation in this research project, nor will you or the your baby be paid. The CPAP used is currently used for all babies in this unit.

4. What does your baby have to do?

To participate in the ÉCLAT study you or your baby will not have to do anything different that you usually would.

5. Other relevant information about the research project

The ÉCLAT will aim to recruit 200 babies over 2 years. Other hospitals may be invited to be involved. The project involves researchers from Monash Newborn, The Royal Women's Hospital and the University of Melbourne.

6. Does your baby have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for your baby to take part, they do not have to. If you decide that they can take part and later change your mind, you are free to withdraw your baby from the project at any stage.

If you do decide that your baby can take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision that your baby can or cannot take part, or that they can take part and then be withdrawn, will not affect their routine treatment, relationship with those treating them, or their relationship with The Site.

7. What are the alternatives to participation?

Your baby does not have to take part in this research project to receive treatment at this hospital. If your baby is not in the study they will receive routine care as per normal.

8. What are the possible benefits of taking part?

We cannot guarantee or promise that your baby will receive any benefits from this research. The results of the study will be important in helping us to look after premature babies in the future, and may change the way we provide breathing support to these babies.

9. What are the possible risks and disadvantages of taking part?

Medical treatments can cause side effects. your baby may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If your baby has any of these side effects, or you are worried about them, talk with your baby's bedside nurse to contact the study investigators or the treating doctor. The investigator will also be looking out for side effects including; Air leak syndromes causing difficulty to breath, injury to the skin/septum around the nose and the usual discomfort some babies find from having prongs in their nose.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the principle investigator/ study doctor/ treating team or bedside nurse immediately about any new or unusual symptoms that your baby gets.

10. What will happen to your baby's test samples?

No physical data/ tissue samples will be collected for this study

11. What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the investigator will tell you about it and discuss with you whether you want your baby to continue in the research project. If you decide to withdraw your

baby, clinical care as usual will continue. If you decide that your baby can continue in the research project, you will be asked to sign an updated consent form.
Also, on receiving new information, the investigator might consider it to be in your baby best interests to withdraw them from the research project. If this happens, the investigator will explain the reasons and arrange for your baby regular health care to continue.

12. Can your baby have other treatments during this research project?
This study will not affect any other treatments/ potential treatments your baby will receive.

13. What if I withdraw my baby from this research project?
If you decide to withdraw your baby from the project, please notify a member of the research team before you withdraw them. This notice will allow that person or the research supervisor to further discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your baby during the research project, the study doctor and relevant study staff will not collect additional personal information, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time of withdrawal will form part of the research project results. If you do not want them to do this, you must tell them before your baby joins the research project.

14. Could this research project be stopped unexpectedly?
This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• The drug/treatment/device being shown not to be effective
• The drug/treatment/device being shown to work and not need further testing
• Decisions made in the commercial interests of the sponsor or by local regulatory/health authorities.

15. What happens when the research project ends?
The results of this research project will be submitted for publication in a medical journal, and also used as part of a thesis towards a postgraduate degree. Both of these formats are made available to the public. A plain language summary of group results will also be made available to you at the end of the trial if you request it.

Part 2 How is the research project being conducted?

16 What will happen to information about your baby?
By signing the consent form you consent to the principle investigator and relevant research staff collecting and using personal information about your baby for the research project. Any information obtained in connection with this research project that can identify your baby will remain confidential. All data and information collected will be stored under a de-identified number only accessible by the research team. The information will be kept for 25 years than destroyed. Only the research team can access this data during this time.
Your baby's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about your baby may be obtained from their health records held at this and other health services, for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your baby's participation in this research project.

It is anticipated that the results of this research project will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that your baby cannot be identified, except with your permission. All individual results will be grouped into their treatment stream, de-identified and not discussed on an individual level.

Information about your baby's participation in this research project will be recorded in their health records.

In accordance with relevant Australian and or Victorian state privacy and other relevant laws, you have the right to request access to your baby's information collected and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your baby's information.

Any information obtained for the purpose of this research project that can identify the participant will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17. Complaints and Compensation

If your baby suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment for your baby. If your baby is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18. Who is organising and funding the research?

This research project is being conducted by Anna Kidman for her Doctor of Philosophy degree. No member of the research team will receive a personal financial benefit from your baby's involvement in this research project (other than their ordinary wages).

19. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Monash Children's Hospital/ The Site Melbourne, Australia.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20. Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if your baby has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study investigator.

Anna Kidman
Monash Newborn
Level 5, Monash Children's Hospital
246 Clayton Road

Dr Risha Bhatia
Monash Newborn
Level 5, Monash Children's Hospital
246 Clayton Road

Clayton 3168
Phone: + 614 238 161 97
+61 3 8572 3737

Clayton 3168
Phone: +61 3 8572 3650

Clinical contact person
If you have any clinical concerns about your baby at any time, you can always speak to your baby's doctor or bedside nurse.

For matters relating to research at the site at which **your baby** is participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	
Telephone	
Email	

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	
HREC Executive Officer	
Telephone	
Email	

Consent Form – Parent/Guardian

Title	*Extubation CPAP Level Assessment Trial*
Short Title	*ÉCLAT*
Protocol Number	*1*
Project Sponsor	*Anna Kidman – PhD study*
Coordinating Principal Investigator/ Principal Investigator	*Anna Kidman & Dr Risha Bhatia (Monash Health)*
Associate Investigator(s)	*Dr Brett Manley (Royal Women's Hospital)* *Dr Rose Boland (Royal Women's Hospital)* *Professor Peter Davis (Royal Women's Hospital)*
Location	*Monash Newborn*

Consent Agreement

I have read the Participant Information Sheet, or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to my baby participating in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

Declaration by Parent/Guardian – for Parent/Guardian who has read the information

Name of Baby (please _____

Name of Parent/Guardian (please _____

Signature of Parent/Guardian _____ Date _____

Declaration - for Parent/Guardian unable to read the information and consent form

Witness to the informed consent process

Name (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Investigator/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation – Parent/Guardian

Title	*Extubation CPAP Level Assessment Trial*
Short Title	*ÉCLAT*
Protocol Number	*1*
Project Sponsor	*Anna Kidman – PhD study*
Coordinating Principal Investigator/ Principal Investigator	*Anna Kidman & Dr Risha Bhatia (Monash Health)*
Associate Investigator(s)	*Dr Brett Manley (Royal Women's Hospital)* *Dr Rose Boland (Royal Women's Hospital)* *Professor Peter Davis (Royal Women's Hospital)*
Location	*Monash Newborn*

Declaration by Parent/Guardian

I wish to withdraw my baby from participation in the above research project and understand that such withdrawal will not affect their routine treatment, relationships with those treating them or the relationship with Monash Children's Hospital – The Site .

Name of Baby (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date_____

Declaration by Investigator/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Investigator Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.
Note: All parties signing the consent section must date their own signature.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	11
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	1,10,11

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4,5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8,9

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	5

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A no long term follow-up
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	4
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	4
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	4
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	10

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9,10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7,8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	2
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	15
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Notes:

- 18b: N/A no long term follow-up The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 03. February 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai