Neurodevelopmental outcome after standard dose sevoflurane versus low-dose sevoflurane/dexmedetomidine/remifentanil anaesthesia in young children

The TREX Trial

Statistical Analysis Plan for the short term outcomes (babyTREX)

1.0
18th September 2023

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List of Abbreviations

AE	Adverse Event
BP	Blood pressure
CI	Confidence Interval
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
ETCO2	End tidal carbon dioxide concentration
ETsevo	End tidal sevoflurane concentration
ETT	Endotracheal tube
GABAA	gamma-Aminobutyric acid A
GCP	Good Clinical Practice
HR	Heart rate
ITT	Intent-To-Treat
IV	Intravenous
LMA	Laryngeal Mask
MAC	Minimum alveolar concentration
MAP	Mean Arterial blood Pressure
NDNMB	Non Depolarising Neuro Muscular Blocker
PACU	Post Anaesthetic Care Unit
REMI	remifentanil
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SpO2	Oxygen saturation
SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. ADMINISTRATIVE INFORMATION

Protocol: 1.9; version 1.9; 01 December 2020
World Health Organization Universal Trial Number: <identifier>
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1.1 Document Version History

Version Date	Version	Author	Signature	Change Description	Reason/Comment
18th September 2023	1.0	Rita Saynhalath		Initial release. Rita Saynhalath Rita Saynhalath (Oct 3, 2023 07:27 CDT)	Not applicable.
		Justin Skowno			
		Nicola Disma		Nicola Disma Nicola Disma (Oct 3, 2023 10:17 GMT+2)	

1.2 Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

Name	Role on Study	Affiliation	Signature	Date
Andrew Davidson	Principal Investigator	Royal Children's Hospital	A Davidson A Davidson (Oct 3, 2023 17:38 GMT+11)	Oct 3, 2023
Katherine Lee	Trial Statistician	Murdoch Children's Research Institute	KJLee KJLee (Oct 3, 2023 20:42 GMT+11)	Oct 3, 2023

2. STUDY SYNOPSIS

TREX is a Phase III randomised, active controlled, parallel arm, assessor blinded, multicentre, superiority trial comparing

1. **Low-dose** - low-dose sevoflurane/ dexmedetomidine/remifentanil anaesthesia, and
2. **Standard-dose** - standard dose sevoflurane anaesthesia.

At trial design, we planned to randomise 450 infants aged less than 2 years of age scheduled for anaesthesia expected to last 2 hours or longer 1:1 to either the low-dose or standard dose arm.

The trial was expected to run for 7 years from the start of participant screening to the last participant completing the study. Recruitment was expected to take 4 years. The follow up period was 3 years. Participants were recruited from 20 sites.

The primary objective of the TREX trial was to determine if, in children less than 2 years of age having anaesthesia expected to last 2 hours or longer, low-dose sevoflurane/dexmedetomidine/remifentanil anaesthesia is superior to standard dose sevoflurane anaesthesia in terms of the global cognitive function as assessed by the full scale IQ score of the Wechsler Preschool and Primary School Intelligence Scale assessed at 3 years of age.

In this SAP, we outline the analysis plan for the short-term outcomes of the TREX trial.

2.1. Objectives Related to the Short-Term Outcomes

The objectives related to the short-term outcomes were to compare the following in children under the age of 2, receiving low-dose sevoflurane/dexmedetomidine/remifentanil anaesthesia versus standard dose sevoflurane anaesthesia when anaesthesia is expected to last 2 hours or longer:

1. Incidence of intra-operative hypotension (intra-operative is defined as the time from induction of anaesthesia until removal of airway)
2. Incidence of intra-operative bradycardia
3. Incidence of intra-operative events of light anaesthesia
4. Incidence and extent of post-operative pain
5. Time to recovery
6. Morbidity and mortality outcomes by 5 days post-operatively including: postoperative readmission, prolonged hospitalization, serious morbidity (resulting in persistent or significant disability), occurrence of life-threatening events, and death

.

2.2. Study Population

Participants were 450 male or female children less than 2 years of age scheduled for anaesthesia expected to last 2 hours or longer. They were recruited from tertiary children's hospitals located throughout Australia, Italy, and the United States.

Eligibility Criteria

Participants were assigned to a randomised study treatment only if they met all the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria

- Younger than 2 years (chronological age)

- Scheduled for anaesthesia that is expected to last at least 2 hours (and/or total operating room time is scheduled to be at least 2.5 hours)
- Has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf.

Exclusion criteria

- Known neurologic, chromosomal or congenital anomaly which is likely to be associated with poor neurobehavioural outcome
- Existing diagnosis of behavioural or neurodevelopmental disability
- Prematurity (defined as < 36 weeks gestational age at birth)
- Birth weight less than 2 kg.
- Congenital cardiac disease requiring surgery
- Intracranial neurosurgery and intracranial craniofacial surgery (isolated cleft lip is not an exclusion)
- Previous cumulative exposure to general anaesthesia exceeding 2 hours
- Planned future cumulative exposure to anaesthesia exceeding 2 hours before the age of 3 years.
- Any specific contra-indication to any aspect of the protocol
- Previous adverse reaction to any anaesthetic
- Circumstances likely to make long term follow-up impossible
- Living in a household where the primary language spoken at home is not a language in which we can administer the Wechsler Preschool and Primary School Intelligence Scale
- Planned postoperative sedation with any agent except opioids (e.g. benzodiazepines, dexmedetomidine, ketamine, barbiturates, propofol, clonidine, chloral hydrate, and other non-opioid sedatives). For example, if such sedation is planned for post-operative ventilation.

2.3. Intervention

Low-dose - After induction the child received a loading dose of 1mcg/kg of dexmedetomidine over 10 minutes followed by an infusion of dexmedetomidine at 1 mcg/kg/hr, and a loading dose of remifentanil 1 mcg/kg over 2 minutes followed by an infusion starting at 0.1 mcg/kg/min or greater. The loading doses were started immediately after induction (or as soon after induction as practicable) and completed within 10 minutes of induction. Dexmedetomidine was discontinued 10 minutes before the end of surgery and remifentanil after last stitch/dressing was applied.

After induction and after dexmedetomidine loading was completed, the child received sevoflurane aiming for an end tidal concentration of 0.6 -0.8% or less. Sevoflurane was discontinued after last stitch and/or dressing applied. Morphine or other long lasting opioids were administered 15 minutes prior to end of the case at the discretion of the anaesthetist.

Standard-dose - After induction the child received sevoflurane aiming for an end tidal concentration of 2.5-3.0% or greater. Sevoflurane was discontinued after last stitch and/or dressing applied. Opioids (apart from remifentanil) were administered at the discretion of the anaesthetist. Dexmedetomidine was not be given to this cohort.

2.4. Randomisation and Blinding

Participants were randomised to either low dose or standard dose in a 1:1 ratio. The treatment allocation was computer generated by an independent statistician using block randomisation (block

sizes 2 and 4), stratified by site and age at exposure (less than 12 months and greater than 12 months). The treating anaesthetist were not blinded to treatment arm. The assessing neuropsychologist and parents were blinded to treatment arm.

An independent statistician will be unblinded and conduct this analysis. The study statistician will remain blinded until the primary analysis is conducted.

2.5. Sample Size

The planned sample size was based on the primary objective of the trial: to determine if low-dose sevoflurane/dexmedetomidine/remifentanil anaesthesia was associated with superior neurodevelopmental outcome based on the global cognitive function as assessed by the full scale IQ score of the Wechsler Preschool and Primary School Intelligence Scale assessed at 3 years of age compared to standard dose sevoflurane anaesthesia when anaesthesia is expected to last 2 hours or longer. In a normal population the Wechsler composite cognitive score (full scale IQ) has a mean of 100 and a standard deviation (SD) of 15. Any difference less than one third of a standard deviation (5 points) would be regarded as being minimally clinically significant. 190 children in each arm were required to have a 90% power to detect a difference of 5 points based on a two-sided test with alpha=0.05. We planned to recruit a total of 450 children to allow for 15% loss to follow up. In a previous trial (the GAS trial) we had a retention rate at 2 years of greater than 85%. This is consistent with other similar studies. There was no sample size conducted around the short-term outcomes explored in this SAP.

2.6. Study Procedures

Baseline demographic data were collected prior to randomisation including: age, birth weight, multiple pregnancy, weight at time of surgery, gender, gestational age at birth, any prior medical history and indication for surgery. Primary language at home, maternal education, maternal age, family structure, rurality, ethnicity, birth order and number of siblings were also collected.

Prior to anaesthesia, systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate (HR), and oxygen saturation were recorded.

During anaesthesia, the dose and timing of all drugs given, and details of end tidal agent concentrations and infusion rates were recorded every 3 minutes. Systolic Blood Pressure(SBP), Mean Arterial Pressure(MAP), end-tidal carbon dioxide concentration (ETCO2), heart rate (HR), temperature and oxygen saturation (SpO2) were noted every 3 minutes during anaesthesia. Any hypertensive or bradycardia event requiring treatment, or any episode of light anaesthesia requiring intervention were noted along with the intervention/treatment used. Where possible, intra-operative data were downloaded in full from the electronic record.

Post-operatively, SBP, MAP, HR, pain score, sedation score and SpO2 were noted every 5 minutes for at least the first 60 minutes following surgery.

Times of induction, start of surgery, end of surgery, removal of airway, arrival in the post anaesthetic care unit (PACU), eye-opening and discharge from PACU were recorded. The details of the surgical procedure(s) were also recorded as well as details of any peri and intra-operative anaesthetic complications.

Families were contacted at 24 hours and at 5 days post-anaesthesia to determine if any major events had occurred.

Neuropsychological tests will be conducted when the child is 3 years of age (chronological age) within a six-month window after their birthday. The assessments will be done either in person or via telehealth. The SAP for these outcomes, including the primary outcome for the trial, will be detailed in a separate SAP.

2.7. Deviations from Protocol

The following will be documented as deviations from protocol:

1. Inappropriate administration or dosage and discontinuation of a medication
2. Safety concern leading to medication administration that does not follow the protocol

Full details of the background to the trial and its design are presented in the protocol.

3. GENERAL STATISTICAL METHODOLOGY

3.1. Objectives of Analysis Plan

This analysis plan covers the analysis of the objectives related to the short-term outcomes within the TREX trial detailed in section 2.1, namely the outcomes during or within 5 days of surgery. The analysis of the objectives related to the longer-term (5-year) outcomes, including the primary objective, will be addressed in a separate SAP.

3.2. Analysis Software

Data with be analysed using Stata v18.0.

3.3. Data verification

Data will be entered directly by study sites into a REDCap database. Any values out of the reference range will be checked by the Data Coordinating Centre in Melbourne and validated by the site. Once all data entry and in-house verification are complete, an unblinded statistician within the Clinical Epidemiology Unit at the Murdoch Children's Research Institute will conduct some specifically programmed data validation checks to ensure the outcomes entered are consistent and accurate.

3.4. Definition of Baseline

Baseline refers to data collected prior to induction of anaesthesia.

3.5. Definition of analysis populations

The population of interest in this SAP is a modified intention to treat (ITT) population. This consists of all participants who were randomised according to the arm in which they were randomised too, irrespective of the intervention received or whether they complete the study, excluding participant who did not have the surgery done (cancellation), hence no intervention was involved. Excluding these participants will not induce bias as surgery cancellation is independent of the treatment arm. Excluded participants will be included in the CONSORT flow chart of the final manuscript but will be excluded from the analysis.

3.6. Definitions related to Adverse Events (AEs)

The study is being conducted in Australia under the CTN scheme. All sites outside Australia are responsible for ensuring that they satisfy their local ethics/Institutional Review Board (IRB) reporting requirements regarding Adverse Event (AE) reporting. However, given the study is being conducted in the U.S. under FDA IND 118058, the AE reporting requirements for the IND also need to be satisfied. A study AE reporting manual has been developed to aid each site with reporting.

AE definitions are as follows:

Term	Definition
Adverse Event (AE)	Any untoward (e.g. unfavourable, negative, or harmful) medical occurrence associated with the use of a drug in

	humans, whether or not considered drug related. An AE can be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of the drug.
Serious Adverse Event (SAE)	An AE that: 1) results in death 2) is life-threatening (the subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred), 3) requires inpatient hospitalisation or prolongation of existing hospitalisation, 4) results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, 5) is an important Medical Event that may jeopardise the subject or may require medical/surgical intervention to prevent one of the serious adverse event outcomes. The interpretation of whether or not an event fulfils this particular criterion is the responsibility of the site investigator.
Suspected Adverse Reaction (SAR)	Any AE for which there is a reasonable possibility that the drug caused the event, meaning the event is possibly, probably, or definitely related to the study drug.
Adverse Reaction (AR)	Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event. .
Suspected unexpected serious adverse reaction (SUSAR)	An SAE: 1) where there is at least a reasonable possibility of a causal relationship between a medicinal product and an adverse event. Put another way, the relationship of the SAE to the study drug cannot be ruled out. 2) that is unexpected, meaning that the nature or severity of the reaction is not consistent with the applicable scientific information (e.g. Investigator's Brochure for an unapproved investigational product or Product Information document or similar for an approved, marketed product).
Significant Safety issue (SSI)	Issue that adversely affects the safety of participants or the continued ethical acceptability or conduct of the trial.
Urgent Safety Measure (USM)	Type of SSI where the Sponsor or Investigator acts immediately to protect participants from an immediate hazard to their health or safety

Monitoring AEs requires that they be classified as to seriousness, expectedness, and potential relationship to the study drugs, all of which drive the reporting process.

a. Expectedness

The purpose of reporting is to provide new, important information on serious reactions or events previously unobserved or undocumented. Therefore, all AEs will be evaluated as to whether their occurrence was unexpected, using the following definitions:

- Unexpected: An unexpected AE or adverse reaction is one for which the nature or severity is not consistent with information in the protocol, consent form, or product brochure. An AE or

adverse reaction also may be categorized as unexpected if the event has not previously been observed at the same specificity and/or severity.

- Expected: An event is considered expected if it is known to be associated with the study drug(s) and/or the disease state.

b. Causality

Causality assessment is required to determine which events require expedited reporting. The following criteria will be used to determine causality:

- Not Related: The event is clearly related to other factors, such as the subject's clinical state, or non-study drugs or interventions.
- Possibly Related: The event follows a compatible temporal sequence from the time of administration of the study drug, but could have been produced by other factors such as the subject's clinical state or non-study drugs or interventions.
- Probably Related: The event follows a reasonable temporal sequence from the time of drug administration, and cannot be reasonably explained by other factors such as the subject's clinical state, or non-study drugs or interventions.
- Definitely Related: The event follows a clear temporal sequence from the time of drug administration, and cannot be reasonably explained by other factors such as the subject's clinical state, or non-study drugs or interventions.

3.7. Adjustment for Multiplicity

In this analysis of secondary short-term outcomes, there are no plans to adjust for multiplicity. However, results will be interpreted with caution focussing on the magnitude of the effect and the 95% confidence interval (CI) rather than the p-value.

3.8. Interim Analyses

No interim analyses were performed on any outcome.

3.9. Handling of Missing Data

It is inevitable that some data will be missing. If less than five percent have missing on the majority of the short-term outcomes, then the analysis will be conducted using a complete case analysis on the available data for each outcome. If there is more than five percent of data missing on a number of outcomes or more than 10% missing data on a given outcome then we will consider the causal mechanism behind the missing data and use this to guide the handling of missing data. For example, if we determine that the data are recoverable and that there are variables that are potential associated with missingness or the incomplete variables, then we will use multiple imputation to handle the missing data. Multiple imputation will be conducted using chained equations, including all variables to be used in the analysis and the variables potential associated with missingness or the incomplete variables, generating 50 imputed datasets. In this case, we will also consider the possibility that the data are non-recoverable as a sensitivity analysis. This sensitivity analysis will be conducted using delta-adjusted multiple imputation, where we will add a value (delta) to the imputed values to represent the suspected difference between the observed and missing values. Potential values for delta will be elicited from context experts.

3.10. Estimands

Section 5 and 6 report analytical approaches for the short term outcomes using the estimand framework. An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It has 5 attributes: population, treatment, variable

of interest e.g. outcome, summary measure, and possible intercurrent events (defined as an event that can occur post-randomization and preclude or affect the interpretation of the variable of interest e.g. discontinuation of treatment).

When defining an estimand, it must be made clear how intercurrent events will be handled in the analysis. Different approaches can be taken towards handling intercurrent events and are described below:

i) Hypothetical: a strategy which envisages a scenario in which the intercurrent event would not occur, e.g. if participants had not switched treatment or if death had not occurred

ii) Treatment policy: a strategy which seeks to understand the treatment effect on the variable regardless of the intercurrent event, i.e. an outcome is of interest whether or not the intercurrent event occurred prior to the outcome, e.g. the final outcome is of interest irrespective of whether the participant takes additional medication

iii) Composite: a strategy which considers the occurrence of the intercurrent event as informative about the participants outcome. Under this strategy the intercurrent event is included in the endpoint definition, e.g. classifying the use of rescue medication as failure, in addition to disease progression, in a time-to-event analysis

iv) Principal Stratification: a strategy wherein treatment effects are assessed in the stratum of participants who would have a specific status with respect to the intercurrent event e.g. examining the effect of treatment in participants who would not require rescue medication

v) While-on-treatment: a strategy which considers response to treatment prior to the occurrence of the intercurrent event to be of interest. For repeated measures, values up to the intercurrent event are of interest but not values after the intercurrent event. Generally this strategy is only useful if the duration of treatment is not relevant either because it is not clinically relevant or because the rate of an event or outcome is constant over time e.g. the rate of adverse events, where one assumes a constant hazard.

4. DESCRIPTIVE STATISTICS

4.1. Recruitment and Follow-up

Recruitment and follow-up will be presented using a flowchart reporting:

- Number screened
- Number excluded and reasons for exclusion
- Number randomised, and treatment allocation
- Number discontinued and reasons for discontinuation
- Number who completed the study intervention
- Number analysed

4.2. Baseline Characteristics

Baseline characteristics and clinical data will be summarised using mean and standard deviations (SD) for continuous variables and numbers and percentages for categorical variables, presented separately for the low-dose and standard-dose arms (see Table 1 in section 9.3). The following variables will be included:

- Sex: male, female
- Age, years
- Weight, kg
- American Society of Anesthesiologists Physical Score Status: 1, 2, 3, 4, or 5
- Gestational age at birth, weeks
- Type of airway: endotracheal tube, laryngeal mask airway
- Duration of anaesthetic in minutes
- Pre-medication: none, Acetaminophen, Midazolam
- Neuromuscular blocking agent administered (Y/N)

4.3. Protocol Deviations

The number of participants with one or more protocol deviation will be reported, along with the number of each type of deviation, by randomized arm:

5.1. Inappropriate administration or dosage, or discontinuation of a medication

5.2. Safety concern leading to medication administration that does not follow the protocol

4.4. Compliance

The number of participants who are compliant with their randomized allocation will be presented as the number and proportion within each randomized arm.

4.5. Concomitant Therapies

The use of regional and local anaesthesia was left up to the individual discretion of the treating anaesthetist. This may have a clinical impact on the blood pressure, heart rates and pain scores of these patients. Patients with regional anaesthesia will be analysed by treatment policy, and the numbers and types of regional anaesthesia summarized and presented in Table 1 as part of clinical data.

5. ANALYSIS OF THE OUTCOME(S)

5.1. Main Analysis

Definitions of the short-term outcomes are given in the table below:

#	Outcome	Definition
1	Intra-operative hypotension	Binary outcome Intra-operative is defined as the time from induction of anaesthesia until removal of airway 1=Yes if: - MAP <35mmHg in children weighing less than 5 kilograms or - MAP <40mmHg in children weighing more than 5 kilograms 0= No if: - MAP >=35mmHg in children weighing less than 5 kilograms Or - MAP >=40mmHg in children weighing more than 5 kilograms
1a	Need for pharmacological treatment of intra-operative hypotension	Binary outcome in those had intra-operative hypotension 1=Yes 0=No
2	Intra-operative bradycardia	Binary outcome Intra-operative is defined as the time from induction of anaesthesia until removal of airway 1=Yes if: - HR <90BPM for >1 minute 0=No if: - HR>=90BPM or - HR<90BPM for <= 1 minute
2a	Need for pharmacological treatment of intra-operative bradycardia	Binary outcome in those had intra-operative bradycardia 1=Yes 0=No
3	Intra-operative events of light anaesthesia	Binary outcome Intra-operative is defined as the time from induction of anaesthesia until removal of airway 1=Yes 0=No
3a	Need for pharmacological treatment of light anaesthesia	Binary outcome 1=Yes 0=No

4	Post-operative pain scores (FLACC pain score)	Continuous outcome Post-operative pain assessed at 60 minutes (scale: 0 to 10) after surgery recorded as range, median, and average
4a	Need for postoperative pain medications during 1st 60 min of PACU stay	Binary outcome 1=Yes 0=No
5a	Time to recovery : End of surgery to eye opening	Continuous outcome End of surgery to eye opening time
5b	Time to recovery : Eye opening to discharge from PACU	Continuous outcome Eye opening to discharge from PACU time
6a	Morbidity and mortality outcome: postoperative readmission	Binary outcome Occurring by 5 days post-operatively 1=Yes 0=No
6b	Morbidity and mortality outcome: prolonged hospitalization	Binary outcome Occurring by 5 days post-operatively 1=Yes 0=No
6c	Morbidity and mortality outcome: serious morbidity	Binary outcome Occurring by 5 days post-operatively resulting in persistent or significant disability 1=Yes 0=No
6d	Morbidity and mortality outcome: life-threatening event	Binary outcome Occurring by 5 days post-operatively 1=Yes 0=No
6e	Morbidity and mortality outcome: death	Binary outcome Occurring by 5 days post-operatively 1=Yes 0=No

For each of these outcomes, we outline the primary estimand of interest in the table below.

Population	**Treatment**	**Outcomes**	**Summary Measure**	**Potential intercurrent events**	**Primary post-randomization intercurrent event strategy**
mITT	Initially randomised treatment	Intra-operative hypotension #1 and 1a	Risk difference (95% CI) between treatment arms, adjusted for stratification factors	1. Initiating treatment with rescue medication 2. Dose adjustment 3. Addition of other non-protocol treatments	Treatment Policy for all intercurrent events - all observed values will be used, regardless

				4. Regional anaesthesia (epidural including caudal, spinal)	of whether or not the subject experienced the intercurrent event
		Intra-operative bradycardia #2 and 2a	Risk difference (95% CI) between treatment arms, adjusted for stratification factors		
		Intra-operative events of light anaesthesia #3 and 3a	Risk difference (95% CI) between treatment arms, adjusted for stratification factors		
		Post-operative pain scores #4 and 4a	Mean or risk difference (95%CI) between treatment arms, adjusted for stratification factors		
		Time to recovery #5	Mean difference (95%CI) between treatment arms, adjusted for stratification factors		
		Morbidity and mortality outcomes #6a - 6e	Risk difference (95% CI) between treatment arms, adjusted for stratification factors		

Results will be presented as a mean or risk difference and its 95% confidence interval (CI) using all of the data collected for all individuals. For binary outcomes, the risk difference will be estimated using a generalised linear model (GLM) which will employ a Gaussian family (to avert convergence difficulties with low prevalence outcomes) and an identity link with a random effect to account for the clustering by site, and a fixed effect for the stratification factor of age at exposure (less than 12 months and greater than 12 months).

For continuous outcomes, the mean difference between treatment arms will be estimated using a GLM model which will employ a Gaussian family and an identity link with a random effect to account for the clustering by site, and a fixed effect for the stratification factor of age at exposure (less than 12 months and greater than 12 months).

5.2. Supplementary Analyses

A supplementary analysis will be performed where protocol deviations prespecified as significant intercurrent events are handled using a principal stratification analysis focussing on those without the ICEs.

Population	**Treatment**	**Outcomes**	**Summary Measure**	**Potential intercurrent events**	**Intercurrent event strategy for supplementary analysis**
mITT	Initially randomised treatment	Intra-operative hypotension #1 and 1a	Risk difference (95% CI) between treatment arms, adjusted for stratification factors	1. Initiating treatment with rescue medication 2. Dose adjustment 3. Addition of other non-protocol treatments	Intercurrent events of initiating treatment with rescue medication or addition of other non-protocol treatments will be handled using a hypothetical strategy. Dose adjustment, regional anaesthesia and other minor variations will be handled using a treatment policy strategy as described for the main analysis.
		Intra-operative bradycardia #2 and 2a	Risk difference (95% CI) between		

			treatment arms, adjusted for stratification factors	4. Regional anaesthesia (epidural including caudal, spinal)	
		Intra-operative events of light anaesthesia #3 and 3a	Risk difference (95% CI) between treatment arms, adjusted for stratification factors		
		Post-operative pain scores #4 and 4a	Mean or risk difference (95%CI) between treatment arms, adjusted for stratification factors		
		Time to recovery #5	Mean difference (95%CI) between treatment arms, adjusted for stratification factors		
		Morbidity and mortality outcomes #6a – 6e	Risk difference (95% CI) between treatment arms, adjusted for stratification factors		

For this supplementary analyses, outcome data for participants experiencing the intercurrent events of initiating treatment with rescue medication or addition of other non-protocol treatments to handled using a hypothetical strategy will be deleted, and multiple imputation will be used to handle the missing outcome data. Again, results will be presented as a mean or risk difference and its 95% CI estimates using a GLM model as described for the main analysis.

6. LISTINGS, TABLES AND FIGURES

6.1 List of Listings

Listing 1. Protocol violators and patients with premature discontinuation.
Listing 2. Adverse events.
Listing 3. Serious adverse events.

6.2 List of Tables

Table 1. Baseline characteristics and clinical data stratified by anaesthetic regimen.
Table 2. Incidence of intra-operative anaesthetic complications stratified by anaesthetic regimen.
Table 3. Description of recovery outcomes stratified by anaesthetic regimen.
Table 4. Incidence of adverse events and serious adverse events stratified by anaesthetic regimen.

6.3 List of Figures

Figure 1	CONSORT diagram
Figure 2	Distributions of maximum pain scores

Listing 1. Protocol violators and patients with premature discontinuation.

Record ID	Number of protocol violations	Reason for protocol violation

Listing 2. Adverse events.

Listing 3. Serious adverse events.

Table 1. Baseline characteristics and clinical data stratified by anaesthetic regimen.

	Low-dose	Standard-dose
Sex, n (%)		
Age, years, mean (SD)		
Weight, kilograms, mean (SD)		
Race, n (%)		
Ethnicity, n (%)		
American Society of Anesthesiologists Physical Score Status, n (%)		
Gestational age at birth, mean (SD)		
Type of airway, n (%) Endotracheal tube Laryngeal mask airway		
Duration of anesthetic, minutes, mean (SD)		
Pre-medication, n (%) None Acetaminophen Midazolam		
Neuromuscular blocking agent administered, n (%)		

Table 2. Incidence of intra-operative anaesthetic complications stratified by anaesthetic regimen.

	Low-dose	Standard-dose	Risk difference (95% CI)	p-value
Hypotension				
Remifentanil infusion decreased, yes				
Dexmedetomidine infusion decreased, yes				
Sevoflurane concentration decreased, yes				
Treated with intravenous fluids, yes				
Treated with vasoactive agents, yes				
Blood pressure variability				

Bradycardia				
Treated with atropine or glycopyrrolate, yes				
Dexmedetomidine infusion decreased, yes				
Light anesthesia: hypertension				
Opioid bolus administered, yes				
Remifentanil infusion increased, yes				
Sevoflurane concentration increased, yes				
Light anesthesia: movement				
Neuromuscular blocker agent administered, yes				
Propofol bolus administered, yes				

Table 3. Description of recovery outcomes stratified by anaesthetic regimen.

	Low-dose	Standard-dose	Mean or risk difference (95% CI)	p-value
Pain scores Analgesic agents administered, yes				
Time to eye-opening, minutes				
Time to removal of airway device, minutes				
Duration of PACU stay, minutes				
Discharge within 24 hours, yes				
Subsequent readmission, yes				
Discharge within 5 days, yes				
Subsequent readmission, yes				

Table 4. Incidence of adverse events and serious adverse events stratified by anaesthetic regimen.

	Low-dose	Standard-dose	Risk difference (95% CI)	p-value
Postoperative readmission				
Prolonged hospitalization				
Serious morbidity				
Life-threatening events				
Death				

Figure 1. CONSORT diagram.

Figure 2. Distributions of maximum pain scores

SAP_babyTREX_ analysis_v1.0 Final Version

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