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Abstract

This Statistical Analysis Plan (SAP) details the statistical procedures to be applied for the analysis of data for the multi-center electroencephalography (EEG) study. It consists of a basic description of the study in broad terms and separate sections that detail the methods of different aspects of the statistical analysis, summarized under the following headings 1: Background; 2: Definitions of protocol violations; 3: Definitions of objectives and other terms; 4: Variables for analyses; 5: Handling of missing data and study bias; 6: Statistical analysis of the primary and secondary study outcomes; 7: Reporting of study results; and 8: References. It serves as a template for researchers interested in writing a SAP.

What is already known:

- A Statistical Analysis Plan (SAP) improves reproducibility, transparency, and validity among clinical studies.
- Many grant application and journals now require an SAP as part of the submission package.

What this article adds:

- This example SAP from an actual research study provides a template for investigators interested in writing their own SAP.

Keywords: Statistical analysis plan, SAP, SAP example, SAP template, EEG, isoelectric EEG.
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7/12/18. Added analysis related to PedsQL (quality-of-life) survey.
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OVERVIEW OF THE STATISTICAL ANALYSIS PLAN (SAP)

This SAP details the statistical procedures to be applied for the analysis of data for the multi-center EEG study. This document will consist of a basic description of the study in broad terms (Section 1) and separate sections that will detail the methods of different aspects of the statistical analysis, summarized in this document under the following headings:

Section 1: Background

1. BACKGROUND

1.1 STUDY DESIGN

This study is a prospective, observational, multi-center study. 10-15 sites from 5 countries (Australia, China, The Netherlands, Switzerland, USA) will be involved in the study. The study population is composed of infants and young children up to 36 months of age scheduled for procedures requiring general anesthesia that are expected to last longer than 30 minutes. Patients will be enrolled prior to the procedure and EEG data will be collected from the start to the end of anesthesia care. A Masimo Sedline EEG monitor will be used at each site to obtain 4-channel unprocessed EEG waveforms. These EEG waveforms will be sent to CHOP (Data Coordinate Center) for storage and analysis. The EEG analysis will focus on the prevalence of isoelectric EEG events, which is defined as EEG amplitude less than 20μV for 2 seconds or more, occurring simultaneously across all 4 EEG channels.[1] To identify perioperative factors associated with isoelectric events, the factors listed in section 7 will be recorded and analyzed. To evaluate the association between isoelectric events and quality-of-life after surgery and anesthesia, the Pediatric quality-of-life (PedsQL) survey [2,3] will be given to caregivers on the day of surgery (baseline), 5 days (follow-up 1), and 30 days (follow-up 2) after surgery.

1.2 OBJECTIVES

The primary aim is to determine the prevalence of isoelectric EEG events during anesthesia in infants and young children undergoing surgery. The secondary aim is to identify perioperative factors associated with these isoelectric events and to explore the association of isoelectric events on the patient's quality-of-life.

1.3 SAMPLE SIZE

The planned sample size is based on a previous study where the overall prevalence of isoelectric EEG events was 50% in pediatric patients receiving sevoflurane for anesthetic maintenance.[4] We assumed the prevalence of isoelectric events using propofol infusion for anesthetic maintenance to be similar to sevoflurane, as there are no published studies on this. Setting the confidence interval as 95% and the marginal error as 0.1, we calculated 97 patients. Due to expected age-dependent changes in normal EEG patterns, patient enrollment was stratified into 5 age groups: 0-3, 4-6, 7-12, 13-18, and 19-36 months.[5,6] To ensure adequate precision across the 5 age groups, we multiplied the sample size by 5 (97 * 5= 485). To account for a 25% attrition, the final number of patients for the study was 647 (485 / 0.75 = 647). Assuming 13 participating sites, each site would enroll 50 patients (647/13 = 50). Since both sevoflurane and propofol infusion maintenance groups were expected to have similar prevalence of isoelectric events, the sample size was sufficiently powered to have adequate precision for each maintenance groups with the estimated marginal error of 0.057. An equal number of patients are expected to be enrolled at each site for two reasons: 1) It was a practical solution as each site was capable of handling this number of patients, 2) Site/location was a variable in the secondary analysis and having an equal number of patients at each site would help with the analyses.

1.4 ELIGIBILITY CRITERIA

1.4.1 Inclusion criteria:

1) Infants or young children greater or equal to 36 weeks postmenstrual age (PMA) and up to 36 months postnatal age (inclusive) on the day of study.
2) Patients scheduled to undergo an anesthetic expected to last greater than 30 minutes.
3) Anesthetic maintenance with sevoflurane if using volatile anesthetic or propofol infusion if using total intravenous anesthetic.
4) Expected airway management with a laryngeal mask airway (LMA) or endotracheal tube.

1.4.2 Exclusion criteria:

1) American Society of Anesthesiologist (ASA) physical status greater than 3
2) Structural/anatomical frontal brain malformations or other circumstances that make it difficult to apply the sensor to the forehead.
3) Abnormal EEG by history

4) Surgery above the neck or cardiac, brain, or emergency surgery.
5) Known allergy or adverse reaction to electrocardiogram adhesives.
6) Currently or recently (discontinued <24 hours ago) on a sedative infusion, such as propofol, morphine, fentanyl, midazolam, dexmedetomidine, or ketamine.
7) Received ketamine within 8 hours prior to the induction of general anesthesia

1.5 DURATION AND SAFETY OF STUDY

Study participation begins with filing out the baseline PedsQL survey and ends with the completion of the 2nd followup PedsQL survey. Patients' caregivers can withdraw their child from the study at any time. Given that this is an observational study with minimal risk, there are no guidelines for stopping the study early and safety data, if applicable, will be summarized.

2. DEFINITION OF PROTOCOL VIOLATIONS

A protocol violation will occur if the patient does not have at least 30 minutes of recorded and interpretable EEG waveform during the anesthetic.

3. DEFINITIONS OF STUDY OBJECTIVES AND OTHER TERMS

3.1 PRIMARY STUDY OBJECTIVE

To identify the prevalence and characterize the length of isoelectric EEG events in infants and young children up to and including 36 months of age, undergoing general anesthesia for greater than 30 minutes. The following five endpoints will be used to describe the isoelectric EEG events.
1) Occurrence of isoelectric EEG events; 2) Total number of isoelectric EEG events; 3) Total duration of all isoelectric EEG events; 4) Mean duration of each isoelectric event; and 5) Percentage of total isoelectric time over total anesthesia time.

3.2 SECONDARY STUDY OBJECTIVES

To identify perioperative factors associated with the occurrence of isoelectric EEG events. These factors include patient, institutional, anesthetic, surgical, and physiological factors, described in section 4.1. Also, to determine if the presence of isoelectric events is associated with changes in quality-of-life scores after surgery.

3.3 DEFINITION OF STUDY TIME PERIODS

While EEG will be recorded during the entire anesthetic course, the following four time periods are defined to characterize the anesthetic and surgical process during EEG recording. *Induction* is from start of anesthetic induction to intubation; *Pre-incision* is from intubation to incision; *Surgery* is from incision to last stitch; and *Post-surgery* is from last stitch to extubation.

3.4 DEFINITION OF OTHER TERMS

Isoelectric EEG Event: EEG amplitude < 20μV (between ±10μV) for 2 seconds or more.[1]

Gestational Age at Birth: Calculated as 40 weeks – (Expected Date of Delivery – Date of Birth).

Prematurity: Born before 37 weeks' gestation.

Postmenstrual Age (PMA) on surgery day: For full term infant: PMA (in weeks) = 42 weeks + postnatal age (weeks) on surgery day. For a premature infant: PMA (in weeks) = (42 weeks – number of weeks born premature) + postnatal age (weeks) on surgery day.

Hemodynamic Observations: Arterial blood pressure will be measured at least once every 5 minutes, peripheral capillary oxygen saturation (SpO2) and heart rate will be measured at least once every minute.

Mild Hypotension: Defined as a mean arterial pressure (MAP) of 36 to 45 mmHg or systolic blood pressure (SBP) of 51 to 60 mmHg for 0-6mo and MAP of 41 to 50 mmHg or SBP of 61 to 70 mmHg for 7-36mo, lasting greater than 3 minutes.[7,8]

Moderate Hypotension: Defined as a MAP of 26 to 35 mmHg or SBP of 41 to 50 mmHg for 0-6mo and MAP of 31 to 40 mmHg or SBP of 51 to 60 mmHg for 7-36mo, lasting greater than 3 minutes. [7,8]

Severe Hypotension: Defined as a MAP less than 26 mmHg or SBP less than 41 mmHg for 0-6mo and MAP less than 31 mmHg or SBP less than 51 mmHg for 7-36mo, lasting greater than 3 minutes. [7,8]

Mild Low Arterial Saturation: Defined as a low arterial saturation event lasting greater than 3 minutes with a peripheral capillary oxygen saturation (SpO2) 80-89%.

Moderate Low Arterial Saturation: Defined as a low arterial saturation event lasting greater than 3 minutes with a SpO2 70-79%.

Severe Low Arterial Saturation: Defined as a low arterial saturation event lasting greater than 3 minutes with a SpO2 < 70%.

Hemodynamic Observations (SBP, MAP, SpO2, Heart rate): The mean (SD) or median(IQR) of hemodynamic values during anesthesia will be derived from the mean values during the four time periods defined in section 3.3 (induction, pre-incision, surgery, and post-surgery). Additionally, for SBP, MAP, and SpO2, the percentage of mild, moderate, and severe hypotension/hypoxia will also be recorded for each of the four time periods.

Blindness: All sites will be blinded. Anesthesia providers in the operating room will not able to view the EEG during the study.

4. VARIABLES FOR ANALYSES

Independent variables that will be used in predictive models:

4.1 Patient Factors

- Gender (M/F)
- Age at study (months)
- Prematurity: Birth < 37 weeks (yes/no)
- Weight at surgery (kg)

- ASA physical status (1, 2, 3)
- Ethnic group, if applicable to the site.

4.2 Institutional Factors

- Site

*4.3 Anesthetic Factors (*Dosages will be recorded where applicable)

- Anesthetic induction technique (inhalational vs. intravenous)
- Use of neuromuscular blockade (yes/no)
- Use of opioids (yes/no)
- Use of nitrous oxide (yes/no)
- Use of ketamine (yes/no)
- Use of midazolam premedication(yes/no)
- Use of propofol bolus (yes/no).
- Airway management: LMA vs. endotracheal tube.
- Maintenance anesthetic technique: inhalational sevoflurane vs. propofol infusion, opioids (yes/no), dexmedetomidine (yes/no), regional anesthesia (yes/no/type).
- Depth of anesthesia during maintenance phase: end tidal sevoflurane concentration (%), IV propofol infusion rate ($mcg \cdot kg^{-1} \cdot min^{-1}$)
- Induction behavior score: 1=calm and controlled, 2=tearful and/or withdrawn, and 3=loud vocal resistance and/or physical resistance requiring physical restraint.[9]
- Emergence delirium score using modified Watcha scale[10, 11]: 1=calm or asleep, 2=not calm, but can be consoled, 3=crying, cannot be consoled, and 4=thrashing and inconsolable. The patient will be assessed for 15 minutes after arriving to the post-anesthesia recovery unit (PACU).
- Discharge ready: The time (minutes) it takes from arrival to the PACU to when the patient is ready for discharge from the PACU.

4.4 Surgical Factors

- Type of surgery: general; otolaryngology; urologic; orthopedic; spine; others.

4.5 Physiological Factors

The mean of the following observations would be calculated for each patient during each phase of anesthetic.

- SpO2 (%)
- SBP (mmHg)
- MAP (mmHg)
- Heart rate (beats per minute)
- Temperature (degrees in Celsius)
- End tidal carbon dioxide concentration-etCO2 (mmHg)

Severity of hypotension and low arterial saturation will be classified as none, mild, moderate, or severe, based on definitions in section 3.4. These classifications are exclusive; once a patient meets criteria for "severe", they will not also be classified as "mild" or "moderate".

Dependent variable:

4.6 PedsQL quality-of-life survey

Based on the patient's age, an age-appropriate pediatric quality-of-life survey will be given to the caregiver on the day of surgery, 5 days and 30 days after surgery. Each question is answered on a 5-point scale; the lower the score, the better the "quality-of-life".[12] The analysis to determine predictors of quality-of-life after surgery will be stratified by age group since the scoring differs for each age group. The survey consists of questions in the following groups.

- Survey for 1-12mo: 36 questions divided into Physical Functioning (6), Physical Symptoms (10), Emotional Functioning (12), Social Functioning (4), and Cognitive Functioning (4).
- Survey for 13-24mo: 45 questions divided into Physical Functioning (9), Physical Symptoms (10), Emotional Functioning (12), Social Functioning (5), and Cognitive Functioning (9).
- Survey for 24+mo: 27 questions divided into Physical Functioning (8), Emotional Functioning (5), Social Functioning (5), School Functioning, if applicable (3), and Cognitive Functioning (6).

5. HANDLING OF MISSING DATA AND STUDY BIAS

There are different potential sources of missing data in this study. Missing data can occur prior to the induction of anesthesia if baseline vital signs are not all captured. Missing data can also occur during periods of the surgery in which vital signs (MAP, heart rate, etc.) are not adequately recorded, such as when a blood pressure cuff cycles for several minutes prior to being able to record a blood pressure. Missing data could also occur with incomplete responses to the repeated surveys of quality-of-life. The missing data in this study is primarily due to documentation and follow-up issues, and will be treated as missing.

To assess the risk of bias due to missingness, we will conduct a sensitivity analysis to determine if the non-evaluable patients (those who do not have valid EEG recordings) are different from the evaluable ones (those who do) in demographic characteristics or medical conditions.

6. STATISTICAL ANALYSIS OF THE PRIMARY AND SECONDARY STUDY OBJECTIVES

6.1 PRESENTATION OF BASELINE DATA

Baseline and demographic characteristics will be summarized by standard descriptive statistics (e.g. means (SD) or median (IQR) for continuous variables such as age, and percentages for categorical variables such as gender).

6.2 ANALYSIS OF THE PRIMARY STUDY OBJECTIVE

The primary analysis will include all subjects meeting inclusion and exclusion criteria and completing the study. The primary endpoints will be analyzed using descriptive statistics for the entire anesthetic procedure, and by each anesthetic phase.

It will be reported as the following:

1- Prevalence (percent) of isoelectric EEG events
2- Median(IQR) of total number of isoelectric EEG events
3- Median(IQR) of total duration of all isoelectric EEG events.
4- Median(IQR) of mean duration of each event.
5- Median(IQR) of percentage of isoelectric time over anesthetic time.

6.3 ANALYSIS OF SECONDARY STUDY OBJECTIVES

A binary outcome variable will be created for the presence of an isoelectric EEG event (yes/no) based upon the criteria defined in the primary objective. To identify the perioperative factors associated with isoelectric EEG events, Chi-square or Fisher's exact test will be used to for categorical variables, while two-tailed independent samples t-test or Wilcoxon-Rank-Sum test will be used for continuous variables, as appropriate. We will accept a Type I error rate (α)up to 0.05.

We will then select the variables from bivariate analysis with p value < 0.1 for multivariable logistic model to adjust for confounding issue. Generalized Estimating Equation (GEE) analysis will be used to account for within-site clustering of the presence of isoelectric events.

To test the association between isoelectric EEG events and PedsQL (quality-of-life) survey results, a multi-level analysis will be performed, accounting for the clustering effect of study site and repeated measures of PedsQL. The primary predictor will be isoelectric events (yes/no). We will also model follow-up time as a predictor and the interaction effect between time and presence of isoelectric events to show the pattern of change over time for each group. If the interaction between isoelectric events and time is significant, those who experienced an isoelectric event will be separately analyzed. In the subset follow-up analysis, we will use percentage of time in isoelectric EEG as a primary predictor of quality-of-life scores. Quality-of-life score could be affected by factors besides isoelectric events. These factors include, but are not limited to ASA physical status, depth of anesthesia, severity of hypotension, type of surgery, and can confound the effects of isoelectric events on quality-of-life. Therefore, we will assess the relationship between baseline (on surgery day) quality-of-life score and these factors using two-sample t-tests, ANOVA, Pearson correlation coefficients, or nonparametric alternatives such as Wilcoxon-Rank-Sum, Kruskal-Wallis ANOVA, or Spearman rank correlations, as appropriate. The factor will be added as a covariate into the model if the p value of the test is less than 0.1.

To account for loss to follow-up, sensitivity analysis using patients with complete follow-up measures of PedsQL will be done to check the robustness of results.

7. REPORTING OF STUDY RESULTS

Table 1. Patient demographic information

Patient Characteristics	All patients (n)	Isoelectric EEG=yes (n)	p value
Age (mean ± SD)			
Weight (kg) (mean ± SD)			
ASA Physical Status n(%)			
1			
2			
3			
Male n(%)			
Post menstrual age (mean ± SD)			
Prematurity n(%)			

Table 2. Intra-operative variables

Intra-operative variables	All Patients (n)	Isoelectric EEG=yes (n)	p value
Type of Surgery n(%)			
Otolaryngology			
General			
Spine surgery			
Orthopedic			
Urologic			
Others			
Premedication n(%)			
Midazolam (yes/no)			
Dexmedetomidine (yes/no)			
Others (yes/no)			
Induction management n(%)			

Sevoflurane (yes/no)			
Propofol (yes/no)			
Dosage of propofol (median(IQR))			
Neuromuscular blockade (yes/no)			
Opioids (yes/no)			
Dosage of opioids in morphine equivalent (mg/kg) (median(IQR))			
Nitrous oxide (yes/no)			
Ketamine (yes/no)			
Dosage of Ketamine (median (IQR))			
Maintenance Type n(%)			
Sevoflurane / Propofol infusion			
Sevoflurane dosage % (median(IQR))			
Propofol infusion dosage mcg/kg/min (median(IQR))			
Total opioid dose in morphine equivalent (mg/kg).			
Airway Management n(%)			
Laryngeal mask airway			
Endotracheal tube			
Regional anesthesia n(%)			
Regional (yes/no)			
Type of block (Neuraxial vs non-neuraxial)			

** More categories for types of surgeries and anesthetics as well as other categorized factors may be added as necessary **

Table 3**.** EEG and physiological data for each time period.

	Induction	**Pre-incision**	**Surgical**	**Post-surgical**	**Total**
Isoelectric EEG events					
Prevalance n(%)					
Total number (median(IQR))					
Total duration (sec) (median(IQR))					
Average duration (sec) (median(IQR))					
Percentage of isoelectric EEG/total time					

(median(IQR))					
Average physiologic data (mean+/-SD or median(IQR))					
SpO2 (%)					
Systolic blood pressure (mmHg)					
Mean arterial pressure (mmHg)					
Heart rate (beats per minute)					
Temperature (Celsius)					
etCO2 (mmHg)					
Severity of hypotension n(%)					
No hypotension					
Mild hypotension					
Moderate hypotension					
Severe hypotension					
Severity of low arterial saturation n(%)					
No low arterial saturation					
Mild low arterial saturation					
Moderate low arterial saturation					
Severe low arterial saturation					

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