Statistical Analysis Plan – Ian Yuan & Bingqing Zhang. Ver 2. Apr 2024.

Title: EEG to monitor propofol anesthetic depth in infants and toddlers

Timeline:

IRB protocol, SAP: May 2022

Patient recruitment: Feb 2023-June 2024

Data cleaning: June 2024– Aug 2024

Data analysis: June 2024– Sept 2024

Manuscript draft: Sept 2024-Nov 2024

Revision History:

SAP revision to Ver 2.- Apr 2024

Background:

Propofol anesthesia in infants is gaining popularity due to fewer respiratory complications, less post-operative nausea vomiting and emergence delirium, compared to sevoflurane. However, unlike sevoflurane, the pharmacodynamics of propofol is less studied in infants and toddlers, particularly the biomarker for propofol brain effect site concentration (Ce), indicative of anesthetic depth. The lack of a real-time biomarker often results in over- or under-dosing of propofol in clinical practice. EEG has been used can be used as a real time biomarker in adults and older children, but the correlation between clinical response to stimuli *vs* EEG *vs* propofol plasma concentration is unknown in infants and toddlers.

Study Aims / Research questions:

1. What is the EEG Spectral Edge Frequency (EEG SEF95) where 50% of the patients under propofol anesthesia (median effective) do not respond to each stimulus (i.e. placement of oral pacifier, electrical stimulation, and laryngoscopy).
2. What is the EEG Spectral Edge Frequency (EEG SEF95) where 90% of the patients under propofol anesthesia do not respond to each stimulus (i.e. placement of oral pacifier, electrical stimulation, and laryngoscopy).
3. What is the association between EEG SEF95 and plasma propofol concentration?

Hypothesis:

1. SEF95 targets vary for the three different stimuli.
2. SEF95 is inversely associated with plasma propofol concentration.

Method

- **Study design:** prospective sequential allocation trial design using Dixon and Mood's up-and-down method.
- **Inclusion & exclusion criteria**
    - Inclusion criteria:
        - Children 3 to 24 months old undergoing surgery.
        - Planned laryngoscopy and endotracheal intubation or laryngeal mask airway (LMA) placement for clinical care.
        - American Society of Anesthesiologist physical status < III.
        - Planned propofol anesthesia for anesthesia maintenance during study period.
        - Muscle relaxant not indicated per planned clinical care for laryngoscopy/intubation or LMA.

    - Exclusion criteria:
        - Patients undergoing cardiac or emergency surgery.
        - Anticipated surgery duration > 2h40m.
        - Known severe neurological disease or diagnosed syndrome associated with abnormal neurological function (might result in abnormal EEG SEF).
        - Deformities of forehead (difficult EEG sensor placement).
        - Known difficult airway.
        - Allergy to propofol.
        - Attending anesthesiologist on record caring for patient plans to administer additional medication besides propofol during study phase.
        - Currently on anti-seizure medication (might alter propofol pharmacodynamics).
        -
- **Aim 1 variable:**
    - Target variable: target EEG SEF95
    - Outcome variable: response to stimuli (yes/no)
- **Aim 2 variable**:
    - Independent variable: plasma propofol concentration
    - Dependent variable: EEG SEF95 at time of blood drawn.
- **Statistical analysis**
  Patient demographical characteristics and baseline medical conditions will be summarized using mean and standard deviation or median and interquartile ranges for continuous variable, while frequency and percent for categorical variables **(table 1).**

1. What is the EEG SEF95 where half of the patients under propofol anesthesia do not respond to each stimulus (i.e. placement of oral pacifier, electrical stimulation and laryngoscopy).

- The analysis will be conducted for each stimulus (i.e. placement of oral pacifier, electrical stimulation and laryngoscopy) and separately for each of 2 age groups (i.e. 3-12 mo, 13-24 mo). At conclusion, there will be a total of six SEF95 values.
- All experimental data will be displayed with sequential dose response graph: patient sequence number will be on the x-axis, their corresponding sequence of target EEG SEF95 will be on the y-axis, and the positive or negative response will be denoted with filled and unfilled circle, respectively **(Fig 1-using mock data).**
- Frequency and observed responses rate will be summarized for each designed target SEF95 level **(table 2).**
- Centered isotonic regression (CIR) model will be used to produce the dose-response curve between SEF95 and response to stimulus. CIR is a nonparametric method that constrains the point estimates to be strictly monotonically increasing or decreasing over the doses. In the absence of strict monotonicity violations, CIR will return the same number of outputs as design points. While when strict monotonicity violation occurs, CIR will return a smaller number of outputs by collapsing the estimates to a sample-size-weighted single point for the involving design points. A shrinkage formula will also be applied to mitigate bias of the isotonic regression estimation at doses away from the target response rate of 50%. Point estimate of response rate and 90% CI will be reported alongside the observed response rate **(Table 2, figure 2-using mock data).**
- The SEF95 at the prespecified response rate (i.e. 50%) will be calculated by taking the inverse of the dose-response function generated using CIR. 90% confidence intervals will be calculated using 'local' approach (i.e. dividing the CI width of response rate at each dose level by the estimate of local slope for the dose-response curve) **(Table 3).**
- Pooled-adjacent-violator algorithm (PAVA) will also be used to produce traditional isotonic regression dose-response estimates as a sensitivity analysis (**figure 2-using mock data).**

2. What is the EEG Spectral Edge Frequency (EEG SEF95) where 90% of the patients under propofol anesthesia do not respond to each stimulus (i.e. placement of oral pacifier, electrical stimulation, and laryngoscopy).
    - The SEF95 at 90% response rate will be calculated from the same CIR model above. 90% confidence interval will be calculated using 'local approach'.
3. What is the association between SEF95 and plasma propofol concentration?
    - The analysis will be conducted for each age group (i.e. 3-12 mo, 13-24 mo).
    - Scatter plot with plasma propofol concentration on y-axis and EEG SEEF95 at the time of blood drawn on x-axis will be generated **(figure 3-using mock data).** Linearity will be assessed using loess curve. Segments or transformation will be applied if the relationship is not linear.
    - If the analysis is conducted for each stimuli, linear regression will be fitted for each stimuli. Fitted line and confidence interval band will be plotted along the scatter plot **(figure 3-using mock data).**

- If the analysis is conducted for all three stimuli together, linear mixed-effect model (LMM) will be conducted to account for within-subject correlation generated from the repeated measures. Both patient-level random intercept and random slope will be added to the model with unstructured variance-covariance structure if appropriate. **(see figure 4 for example-using mock data)**

Table 1. Baseline characteristics of study participants

N	
Age	
Age group, n(%)	
3-12 mo	
12-24 mo	
Gender, n(%)	
Male	
Female	
…	

Table 2. Reponse rate at each designated point

EEG SEF95	Number of total patients	Number of patients with response	Observed response rate	Estimated response rate (95% CI)
8				
10				
12				
14				
16				
18				
…				

Table 3. SEF95 where 50% of the patient will not response to the stimuli

	3 – 12 mo	13-24 mo
Placement of oral pacifier	XX (90% CI)	
Electrical stimulation		
Laryngoscopy		

Fig 1. Sequential dose response graph

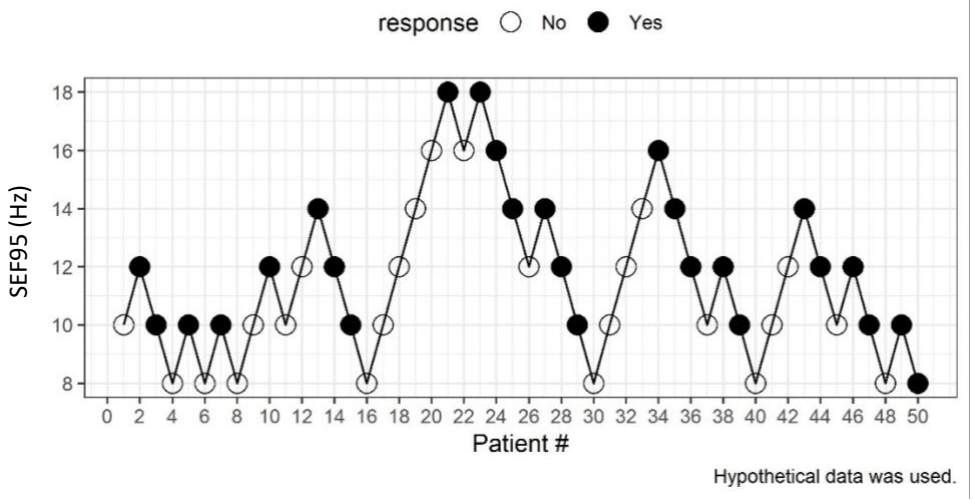

Fig 2. Observed & estimated response rate

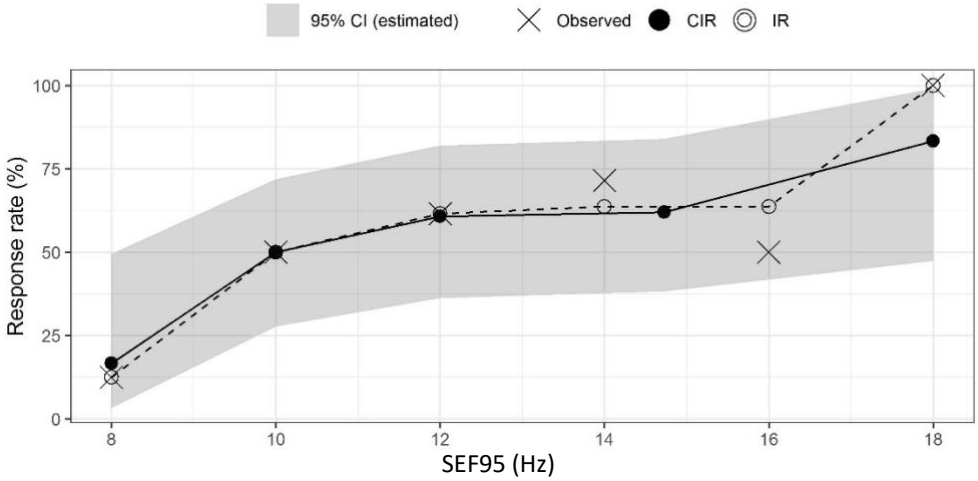

Fig 3: Association between Plasma Propofol

Concentration and EEG SEF95

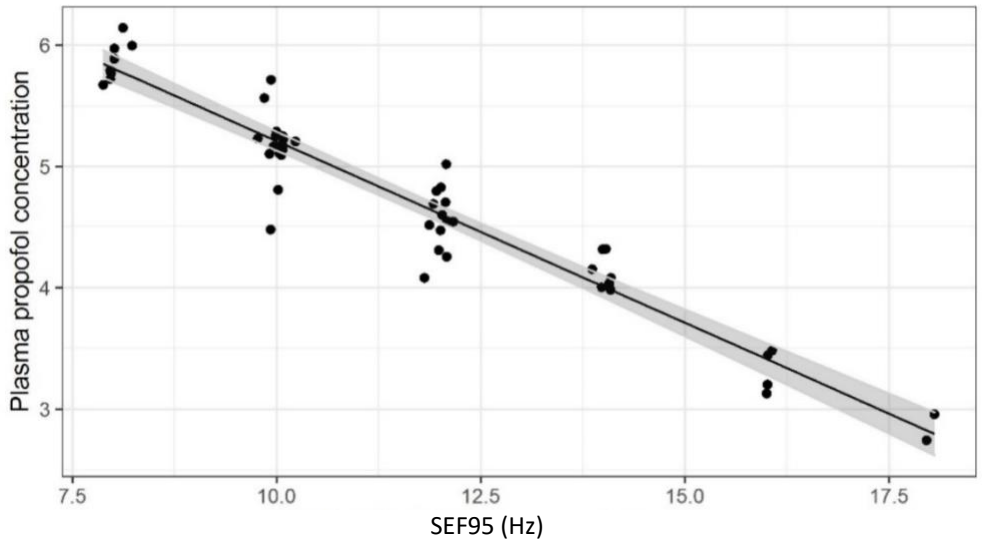

Fig 4. Association between pH and PaCO2 by subjects

Fitted lines are generated from linear mixed-effect model with random intercept and random slope, both average and subject-specific lines are presented