

**Protocol for the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes
(ENGAGES) Study: a Pragmatic, Randomized Clinical Trial**

NCT02241655

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ENGAGES One-Year Outcomes Analysis Plan

Analyses to be completed using R software.

All tests to be 2-sided. P values < 0.05 to be considered suggestive, and P values < 0.005 to be considered as stronger evidence.

Hypothesis 1: Is EEG Guidance Intervention Associated with Reduced One-Year Mortality?

Patient Population: Patients randomized to intervention or control (N = 1232)

Primary Predictor Variable: EEG guidance intervention

(X=0 for control or X=1 for intervention)

Intention to treat

Outcome: Mortality, with one-year follow up

- Any patient who is lost to follow up before one year will be right-censored at the time of last follow-up. (No assumptions are made about vital status after the date of last follow up.)

Data Description Plan: Kaplan-Meier curves, stratified by intervention group

Analysis Plan: Cox proportional hazards regression for one-year mortality

- Will perform unadjusted and adjusted analyses
- Will adjust for age, sex, American Society of Anesthesiologists (ASA) physical status classification (1-2 vs 3 vs 4-5), number of comorbid conditions, baseline poor functional capacity (<4 METS), history of falls (yes/no within previous 6 months), evidence of abnormal cognition (preoperative Short Blessed Test score > 4), surgery type (cardiac versus non-cardiac), length of anesthesia (Anesthesia Stop – Anesthesia Start)
 - o Multiple imputation may be used to address missing values of these variables

Planned Sensitivity Analyses

1. Best-Case Scenario for Missing Data
 - o Assume all patients with missing mortality data in the control group die on the date of last follow-up. Assume all patients with missing mortality data in the intervention group survive to one year.
2. Worst-Case Scenario for Missing Data
 - o Assume all patients with missing mortality data in the control group survive to one year. Assume all patients with missing mortality data in the intervention group die on the date of last follow-up.

Hypothesis 2: Is EEG Guidance Intervention Associated with Improved Quality of Life One Year After Surgery?

Patient Population: Patients randomized to intervention or control (N = 1232)

Primary Predictor Variable: EEG guidance intervention

(X=0 for control or X=1 for intervention)

Intention to treat

Outcomes: Veterans RAND 12-Item Health Survey (VR-12) physical component score (PCS), VR-12 mental component score (MCS), one year postoperatively

- Partially completed VR-12 surveys will not be scored and will be considered missing.

Data Description Plan: Box plots of VR-12 PCS and MCS at baseline, 30 days, and 1 year for the two groups. Provide median, interquartile range, and range at each time point.

Analysis Plan: Generalized linear model

$$y_{365} = \beta_0 + f(y_0) + \beta_1 x + \beta Z + \varepsilon$$

- In this equation, y_{365} is the quality of life (either VR-12 PCS or VR-12 MCS) at one year, and y_0 is the quality of life metric at baseline. x is the EEG guidance intervention ($x=0$ for control or $x=1$ for intervention). Z is a vector of additional variables for which we will adjust.
- $f(y_0)$ is a potentially nonlinear function describing the relationship between baseline quality of life and quality of life at one year. This function will be modeled using splines.
- Will perform unadjusted ($Z = \text{null}$) and adjusted ($Z \text{ not null}$) analyses. Will adjust for age, sex, American Society of Anesthesiologists (ASA) physical status classification (1-2 vs 3 vs 4-5), number of comorbid conditions, baseline poor functional capacity (<4 METS), history of falls (yes/no within previous 6 months), evidence of abnormal cognition (preoperative Short Blessed Test score > 4), surgery type (cardiac versus non-cardiac), length of anesthesia (Anesthesia Stop – Anesthesia Start)
 - o Multiple imputation may be performed to address missing values of these variables
- Any patient with missing quality of life either at baseline or at one year will be excluded.
- $H_0: \beta_1 = 0$ (The null hypothesis is that the EEG guidance intervention has no association with postoperative quality of life.)

Planned Sensitivity Analyses

1. Best-Likely-Case Scenario for Missing Data
 - o For patients missing baseline quality of life, set the baseline quality of life equal to the mean baseline value for the appropriate stratum of the population. Population to be stratified based on type of surgery (cardiac versus non-cardiac) and history of falls.
 - o For patients in the intervention group missing one-year quality of life, set the quality of life value equal to the maximum postoperative quality of life within the patient's stratum (still stratified by type of surgery and history of falls).
 - o For patients in the control group missing one-year quality of life, set the quality of life value equal to the minimum postoperative quality of life within the patient's stratum (still stratified by type of surgery and history of falls).
 - o Patients who die before one year will be excluded.
2. Worst-Likely-Case Scenario for Missing Data
 - o For patients missing baseline quality of life, set the baseline quality of life equal to the mean baseline value for the appropriate stratum of the population. Population to be stratified based on type of surgery (cardiac versus non-cardiac) and history of falls.
 - o For patients in the control group missing one-year quality of life, set the quality of life value equal to the maximum postoperative quality of life within the patient's stratum (still stratified by type of surgery and history of falls).

- For patients in the intervention group missing one-year quality of life, set the quality of life value equal to the minimum postoperative quality of life within the patient's stratum (still stratified by type of surgery and history of falls).
- Patients who die before one year will be excluded.
- 3. Expanded Control Group with Matched Cohort
 - Each patient randomized in the ENGAGES trial will be matched to a patient enrolled in the SATISFY-SOS study.
 - All patients enrolled in SATISFY-SOS who meet the following criteria will be considered.
 - Age 60 or older
 - Hospital stay ≥ 2 days
 - Surgery between January 2015 and May 2018 (same dates as ENGAGES)
 - For each patient meeting the above criteria, a propensity score for enrollment in the ENGAGES trial will be constructed using logistic regression. Covariates included in the model will include age, sex, ASA physical status, surgery type (cardiac versus non-cardiac), and history of falls.
 - (Because all patients enrolled in ENGAGES were co-enrolled in SATISFY-SOS, the population described above will include all patients who were enrolled in ENGAGES.)
 - Patients enrolled in ENGAGES will be matched 1:1 without replacement to SATISFY-SOS patients not enrolled in ENGAGES based on the logit of the propensity score. A greedy nearest-neighbor algorithm will be used, with a maximum caliper width of $0.2 \times$ the standard deviation in the logit of the propensity score.
 - Use the same model structure described above.
 - Add a variable to Z indicating whether the patient was enrolled in ENGAGES.
- 4. Patient-Reported Subjective Quality of Life Change
 - Analysis to include the subset of patients enrolled in ENGAGES who returned the SATISFY-SOS survey at one year
 - The survey includes a question asking if quality of life is better, the same, or worse compared to before surgery
 - Use a chi square test to compare whether patients in the intervention group were more likely to rate their quality of life as "better" the before surgery, compared to patients in the control group.

Hypothesis 3: Is EEG Guidance Intervention Associated with Fewer Falls One Year After Surgery?

Patient Population: Patients randomized to intervention or control (N = 1232)

Primary Predictor Variable: EEG guidance intervention

(X=0 for control or X=1 for intervention)

Intention to treat

Outcomes: Presence or absence of fall(s) during the one-year postoperative follow-up period, measured via patient report on the one-year ENGAGES survey

- Patients who did not fill out the survey (including both living non-respondents and deceased patients) will be excluded

Data Description Plan: Confusion matrix of falls versus EEG guidance intervention

Analysis Plan: Logistic regression

- Will perform unadjusted and adjusted analyses
- Will adjust for age, sex, American Society of Anesthesiologists (ASA) physical status classification (1-3 vs 4-5), number of comorbid conditions, history of falls (yes/no within previous 6 months), evidence of abnormal cognition (preoperative Short Blessed Test score > 4), surgery type (cardiac versus non-cardiac), length of anesthesia (Anesthesia Stop – Anesthesia Start)
 - o Note that ASA is dichotomized in this analysis, and functional capacity <4 METS has been dropped. These changes were made to reduce the number of degrees of freedom in the model, with the goal of having one degree of freedom per 10 patients who fell.
 - o Multiple imputation may be used to address missing values of these variables

Planned Sensitivity Analyses

1. Deceased Patients
 - o Assume all patients who die within one year have fallen.
2. Best-Case Scenario for Missing Data
 - o Assume all patients who die within one year have fallen.
 - o Assume that living patients in the intervention group with missing fall outcome data have not fallen. Assume that living patients in the control group with missing fall outcome data have fallen.
3. Worst-Case Scenario for Missing Data
 - a. Assume all patients who die within one year have fallen.
 - b. Assume that living patients in the intervention group with missing fall outcome data have fallen. Assume that living patients in the control group with missing fall outcome data have not fallen.
4. Expanded Control Group with Matched Cohort
 - o Use the same matched cohort as described above in Hypothesis 2.
 - o Perform a logistic regression as described above, also adjusting for whether the patient was enrolled in ENGAGES.
5. Number of Falls
 - o For patients who completed the SATSIFY-SOS 1-year survey, we have a categorical variable detailing the number of falls (0, 1, 2, or 3+).
 - o Perform an ordinal logistic regression, adjusting for the variables described above.

Exploratory Analyses:

1. Is duration of intraoperative EEG suppression (minutes with suppression ratio > 1%) associated with mortality?
 - a. Cox proportional hazards model, adjusting for same variables as in hypothesis #1
 - b. Instrumental variable analysis will be used to account for the EEG intervention

2. Is duration of intraoperative EEG suppression (minutes with suppression ratio > 1%) associated with worse quality of life at one year?
 - a. Generalized linear model, same structure as in hypothesis #2
 - b. Instrumental variable analysis will be used to account for the EEG intervention
3. Is duration of intraoperative EEG suppression (minutes with suppression ratio > 1%) associated with more falls at one year?
 - a. Logistic regression, adjusting for same variables as in hypothesis #3
 - b. Instrumental variable analysis will be used to account for the EEG intervention
4. Is duration of intraoperative BIS < 40 associated with mortality?
 - a. Cox proportional hazards model, adjusting for same variables as in hypothesis #1
 - b. Instrumental variable analysis will be used to account for the EEG intervention
5. Is duration of intraoperative BIS < 40 associated with worse quality of life at one year?
 - a. Generalized linear model, same structure as in hypothesis #2
 - b. Instrumental variable analysis will be used to account for the EEG intervention
6. Is duration of intraoperative BIS < 40 associated with more falls at one year?
 - a. Logistic regression, adjusting for same variables as in hypothesis #3
 - b. Instrumental variable analysis will be used to account for the EEG intervention
7. Is median intraoperative end-tidal anesthetic concentration value (measured in MAC) associated with mortality?
 - a. Cox proportional hazards model, adjusting for same variables as in hypothesis #1
 - b. Instrumental variable analysis will be used to account for the EEG intervention
8. Is median intraoperative end-tidal anesthetic concentration value (measured in MAC) associated with worse quality of life at one year?
 - a. Generalized linear model, same structure as in hypothesis #2
 - b. Instrumental variable analysis will be used to account for the EEG intervention
9. Is median intraoperative end-tidal anesthetic concentration value (measured in MAC) associated with more falls at one year?
 - a. Logistic regression, adjusting for same variables as in hypothesis #3
 - b. Instrumental variable analysis will be used to account for the EEG intervention
10. Is the EEG guidance intervention associated with higher (better) Barthel Index at one year?
 - a. Will only be available for patients who return the SATISFY-SOS survey
 - b. Mann Whitney U test (because we expect a skewed distribution)
11. Is the EEG guidance intervention associated with a higher rate of return to work at one year?
 - a. Will only be available for patients who return the SATISFY-SOS survey
 - b. Chi-square test for dichotomous return to work (yes/no)
 - c. Among patients who return to work, Mann Whitney U test for number of months before the patient returned to work