ADAPT-2 (Anesthetic Depth and Postoperative Delirium Trial – 2)

A randomized controlled trial to reduce postoperative delirium through reduction in intraoperative EEG suppression in older surgical patients undergoing major noncardiac surgery

Clinical trial number and registry URL: NCT01983384

Version date: July 25, 2018

Principal Investigator:
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Study Application (Version 1.7)

1.0 General Information

***Enter the full title of your study:**

The Effect of Anesthetic Depth on Postoperative Cognitive Outcomes, II

***Enter the study number or study alias**

ADAPT 2
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add Department(s)

2.1 List departments and/or research programs associated with this study:

Primary Dept?	Department Name
◉	**UCSF** - *127037* - M_Anesthesia
○	**UCSF** - *144075* - M_Laboratory Medicine

3.0 Assign key study personnel(KSP) access to the study

3.1 *Please add a Principal Investigator for the study:

Leung, Jacqueline M, MD, MPH

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Kramer, Joel, PsyD
Other Investigator
Lieberman, Jeremy A
Other Investigator

B) Research Support Staff

Tang, Christopher J
Research Assistant

3.3 *Please add a Study Contact:

Leung, Jacqueline M, MD, MPH
Tang, Christopher J

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s):

Gropper, Michael Allan, MD, PhD
Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Qualifications of Key Study Personnel

4.1 November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website.**

List the study responsibilities and qualifications of any individuals who qualify as Key Study Personnel (KSP) at UCSF and affiliated sites ONLY by clicking the "Add a new row" button. This information is required and your application will be considered incomplete without it.

KSP Name	Description of Study Responsibilities	Qualifications
Dr. Leung, Jacqueline M, MD, MPH	Dr. Leung will be the principal investigator and will design and oversee all aspects of the project and coordinate all the research activities. Dr. Leung will direct all pre-, intra-, and post-operative data collection and analysis. This will include all in-hospital and post-discharge outcome data.	Dr. Leung is Professor of Anesthesia & Perioperative Care at the University of California, San Francisco (UCSF). Dr. Leung has extensive experience in designing and conducting clinical trials and outcomes research studies. Her earlier work has focused on areas relating to the importance, detection and therapy of perioperative myocardial ischemia in surgical patients with heart disease, as well as the cardiovascular effects and safety of anesthetics in high-risk surgical patients. After devoting a full sabbatical year

		in 1997-1998 to obtain additional training in epidemiology and biostatistics, which resulted in a Master's degree in Public Health, Dr. Leung now focuses on outcomes research in the geriatric surgical patients. Dr. Leung leads a research team, the Perioperative Medicine Research Group, which consists of postdoctoral research fellows, research associates and students, based at UCSF.
Dr. Kramer, Joel PsyD	Dr. Kramer will help in the study design, particularly in the selection of neuropsychologic tests to be used for the study, and will also consult on all issues relating to neuropsychological testing of the subjects.	Dr. Kramer is a Clinical Professor of Neuropsychology and Neurology and the Director of the Memory and Aging Center Neuropsychology program at UCSF. Dr. Kramer has been extensively involved in studying the cognitive changes associated with brain disorders for the past two decades. He has co-authored widely used neuropsychological measures of memory and executive functioning. Much of his work has been devoted to identifying the different ways in which neurodegenerative diseases affect memory and other abilities and in utilizing these differences to improve differential diagnosis of cognitive disorders.
Lieberman, Jeremy A	Dr. Lieberman will assist with monitoring the anesthetic depth of patients.	Dr. Lieberman is a Clinical Professor of Anesthesia and Perioperative Care at UCSF.
Shalabi, Ahmed M	Dr. Shalabi will assist with monitoring the anesthetic depth of patients.	Dr. Shalabi is an Assistant Clinical Professor of Anesthesia and Perioperative Care at UCSF.
Tang, Christopher J	Mr. Christopher Tang will assist with the recruitment of surgical patients and with preoperative and longterm cognitive testing.	Mr. Temur Kamal is a research associate working under Dr. Leung. He has extensive experience with clinical trials analysis for the project and outcome studies, specifically investigating the pathophysiology of postoperative delirium and cognitive dysfunction in older surgical patients.

5.0 Initial Screening Questions - Updated 9/13

(Note: You must answer every question on this page to proceed).

If you are converting to the new form, check questions 5.4, 5.6, 5.7, 5.8 and 5.10 before saving and continuing to the next section.

5.1 * Application type:

- (•) Full Committee
- ( ) Expedited
- ( ) Exempt

5.2 * Risk level (Help Text updated 9/13):

- ( ) Minimal risk
- (•) Greater than minimal risk

5.3 * Subject contact:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

5.4 * Funding (past or present):

- (•) Funded or will be funded (external sponsor, gift, program or specific internal or departmental funds)
- ( ) Unfunded (no specific funds earmarked for this project)
- ( ) Unfunded student project

5.5 * The Principal Investigator and/or one or more of the key study personnel has financial interests related to this study:

( ) Yes (•) No

If **Yes**, the Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

5.6 * This is an investigator-initiated study:

(•) Yes ( ) No

5.7 * This study ONLY involves retrospective records review and/or identifiable biospecimen analysis:

( ) Yes (•) No

5.8 * This is a clinical trial:

(•) Yes ( ) No

Clinical Trial Registration
"NCT" number for this trial:

NCT01983384

5.9 * This is a multicenter study:

○ Yes ◉ No

5.10 * This application involves the study of unapproved or approved drugs, devices, biologics or in vitro diagnostics:

◉ Yes ○ No

5.11 * This application involves a Humanitarian Use Device:

◉ No
○ Yes, and it includes a research component
○ Yes, and it involves clinical care ONLY

5.12 * This study involves human stem cells (including iPS cells and adult stem cells), gametes or embryos:

◉ No
○ Yes, and requires CHR and GESCR review
○ Yes, and requires GESCR review, but NOT CHR review

5.13 * This is a CIRB study (e.g. the NCI CIRB will be the IRB of record):

○ Yes ◉ No

5.14 * This application includes a request to rely on another IRB (other than NCI CIRB):

○ Yes ◉ No

Note: If this request is approved, the CHR will **NOT** review and approve this study. Another institution will be the IRB of record.

6.0 Funding

6.1 Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor: **Note: we require only a P Number *OR* an A Number for funding coming through UCSF. Please avoid these common errors in funding documentation:**

- **DO NOT add the A Number if a P Number was already provided OR update the A Number field when a new funding cycle begins. The IRB does NOT use this information or want these changes made.**
- **DO NOT add a grant continuation as a new funding source.**

External Sponsor:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)

⊟	NIH Center for Scientific Review	01	UCSF	Grant	P0502184	

Sponsor Name:	NIH Center for Scientific Review
Sponsor Type:	01
Sponsor Role:	Funding
Grant/Contract Number:	1R21AG048456-01A1
Awardee Institution:	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
UCSF RAS "P number" or eProposal number:	P0502184
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	The Effects of Light vs. Deep Anesthesia on Postoperative Cognitive Outcomes
PI Name: (If PI is not the same as identified on the study.)	
Significant Discrepancy:	

Gift, Program, or Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below, if applicable)

List the gift, program, or departmental funding source:

6.2 If you tried to add a sponsor in the question above and it was not in the list, follow these steps:

- **If funding has already been awarded or the contract is being processed by the Office of Sponsored Research (OSR) or Industry Contracts Division (ICD), your sponsor is already in the system and the project has an eProposal Proposal or Award number. Check with your department's OSR Staff or ICD Officer to ask how the sponsor is listed in the UC sponsor list and what the Proposal or Award number is. Click here to find your OSR staff and here to find your ICD staff.**
- **If your sponsor is not yet in the list, enter it in the box below.**

○ Sponsor not in list

Only if your sponsor is not yet in the list, type the sponsor's name:

If the funding is administered by the UCSF Office of Sponsored Research, your study will not receive CHR approval until the sponsor and funding details have been added to your application.

6.3 * This study is currently supported in whole or in part by Federal funding OR has received ANY Federal funding in the past (Help Text updated 9/13):

(●) Yes ( ) No

If **yes**, indicate which portion of your grant you will be attaching:

- [x] The Research Plan, including the Human Subjects Section of your NIH grant or subcontract
- [ ] For other federal proposals (contracts or grants), the section of the proposal describing human subjects work
- [ ] The section of your progress report if it provides the most current information about your human subjects work
- [ ] The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

7.0 Sites

7.1 Institutions (check all that apply):

- [x] UCSF
- [ ] China Basin
- [ ] Helen Diller Family Comprehensive Cancer Center
- [x] Mission Bay
- [ ] Mount Zion
- [ ] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Blood Centers of the Pacific (BCP)
- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno (Community Medical Center)
- [ ] Gallo
- [ ] Gladstone
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)

7.2 Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project (Help Text updated 9/13):

- [ ] Other UC Campus
- [x] Other institution
- [ ] Other community-based site
- [ ] Foreign Country

List the foreign country/ies:

7.3 Check any research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program

8.0 Studies Involving Other Sites

8.1 UCSF is the coordinating center:

○ Yes ◉ No

If **Yes**, describe the plan for communicating safety updates, interim results, and other information that may impact risks to the subject or others among sites:

If **Yes**, describe the plan for sharing modification(s) to the protocol or consent document(s) among sites:

8.2 Check any other UC campuses with which you are collaborating on this research study:

- ☐ UC Berkeley
- ☐ UC Davis
- ☐ Lawrence Berkeley National Laboratory (LBNL)
- ☐ UC Irvine
- ☐ UC Los Angeles
- ☐ UC Merced
- ☐ UC Riverside
- ☐ UC San Diego
- ☐ UC Santa Barbara
- ☐ UC Santa Cruz

8.3 Are the above UC campuses requesting to rely on UCSF's IRB (check all that apply):

- ☐ Yes (Submit a reliance request through the UC IRB Reliance Registry)
- ☐ No (Complete IRB Approval Certification section)

9.0 Outside Site Information

9.1 Outside Site Information

Click "Add a new row" to enter information for a site. Click it again to add a second site again to add a third site, a fourth site, etc.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Virginia Polytechnic Institute and State University

Contact name:

Laura Sands

Email:

lsands@vt.edu

Phone:

514-231-6074

For Federally-funded studies only, corresponding FWA#:

*** The research at this site will be reviewed by:**

- ○ The non-affiliated site's IRB or a private IRB
- ○ The non-affiliated site is requesting UCSF to be the IRB of record for this study
- ◉ The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

10.0 Study Design

10.1 * Study design (Help Text updated 9/13):

The proposed study will include a randomized control trial of 204 older patients undergoing major non-cardiac surgery, who will be randomized to receive processed EEG-guided anesthetic levels during surgery vs. standard care. Assessments will include the 1) measurement of anesthetic depth, measured before and during surgery using an approved anesthetic depth monitor (SEDline), 2) measurement of cognitive status, cognitive function measured pre- and post- operatively while the patients are in the hospital using the Digit Symbol, Word list, Verbal fluency, and Digit Span and also at one month and three months postoperatively by phone using the neurocognitive tests described in the our previously approved studies, this includes the Telephone Interview for Cognitive Status (TICS). Based on studying over one thousand patients, we estimate that it will take 10 minutes for the one month and three month follow-up calls, and 3) screening of delirium using the Confusion Asssessment Method Rating Scale (CAM). The outside collaborator, Dr. Sands from Virginia Polytechnic Institute and State University, will help with data analysis, but will not have access to subject identifiers.

10.2 If this is a clinical trial, check the applicable phase(s) (Help Text updated 9/13):

- ☐ Phase I
- ☐ Phase II
- ☑ Phase III
- ☐ Phase IV

11.0 Scientific Considerations

11.1 Hypothesis (Help Text updated 9/13):

This study has a hypothesis:

(•) Yes ( ) No

If yes, state the hypothesis or hypotheses:

Preoperative level of cognitive function moderates the effect of anesthetic depth on incident delirium or POCD.

11.2 * List the specific aims:

The specific aims of this randomized control trial are:
1. To determine the feasibility and safety of randomizing patients undergoing major non-cardiac surgery to receive processed EEG-guided anesthetic levels during surgery vs. standard care. In this exploratory study, we aim to determine whether processed EEG guided anesthetic management can be practiced uniformly by a number of anesthesia providers across a large group of older surgical patients.
2. To determine an effect size for designing a future larger trial to determine whether anesthetic depth contributes to an increased incidence of adverse postoperative cognitive outcomes as measured by delirium or cognitive decline.
3. To determine whether preoperative level of cognitive function moderates the effect of depth of anesthesia on incident delirium or POCD.

11.3 Statistical analysis:

We will use descriptive statistics to describe the characteristics of the study sample and to compare baseline characteristics in the two treatment groups. We will use two-sample t tests, Mann-Whitney nonparametric tests, chi-square tests, or contingency table tests to compare the demographic and clinical characteristics between the interventional and standard care groups. These analyses serve to validate that randomization was effective. If any characteristics are significantly unbalanced, we will conduct multivariate analyses to adjust for such variables. We will use an intention to treat paradigm in assessing the effect of anesthetic depth on the development of delirium and POCD.
Aim 1. We will test whether assignment to EEG-guided anesthetic management will result in significant differences in PSI scores. Prior to model construction, the total time that the PSI is in the range specified by the protocol in the interventional group will be plotted and transformations will be performed as necessary to meet model assumptions. We will compute a mixed effects model to treat group membership as a fixed effect, the anesthesiologist as the random effect, and the total time that the PSI is in range as the dependent variable. This model will include any patient characteristics known to differ between treatment groups at baseline. When considering the impact of group assignment on autonomic signs, we will construct a variety of models in which the dependent variables are operationalized using a variety of methods including clinically relevant thresholds and variability over time as described in our earlier published work. Again, we will use mixed models as specified above and the distribution associated with the model will depend upon the distributional characteristics of the dependent variable under study. We will determine whether the groups differ in risk for use of vasoactive drugs using mixed a logistic regression model in which anesthesiologist is treated as a random effect, treatment group as a fixed effect and patient characteristics that differ at baseline will be included as covariates. A mixed effect regression model will be used to determine whether quantity of vasoactive agents differ between groups (using appropriate transformations on the dependent variable). Descriptive statistics of anesthesiologist responses to questions about why they could not adhere to the assigned threshold will be calculated for each group.
Aim 2. To test whether assignment to EEG-guided anesthetic depth management affects postoperative cognitive outcomes. The first analysis will use an intention to treat paradigm to determine the effect sizes associated with assignment to the interventional vs. the standard care groups. Chi-square analyses will be conducted to determine the association between group assignment and incident delirium and incident POCD. We will then create PSI categories based on the amount of time the patient was in the prescribed range of PSI (the category cut-offs will be informed both by the distribution of times and clinical relevance). We will determine the association between these PSI categories and incidence of delirium and POCD separately using mixed logistic models with the physician as a random effect. We will also compute longitudinal mixed models in which the dependent variables are the postoperative assessments of delirium severity (using the MDAS) and cognitive function (Word List, Verbal Fluency, Digit Symbol, and Digit Span scores) to determine the association between PSI categories and change in cognition over time.
Aim 3. To determine whether preoperative level of cognitive impairment moderates the effect of EEG-guided anesthesia on incident delirium or POCD. We will construct hierarchical linear models to predict incident delirium or POCD. Those models will include anesthesiologist as a random effect and group membership, preoperative level of cognitive impairment (as defined by the preoperative cognitive test scores) and the interaction between level of cognitive impairment and group membership to determine whether the association between group membership and incident delirium is moderated by preoperative cognitive impairment. We will conduct a similar model using total time in the specified PSI range to

measure the extent to which baseline cognitive functioning moderates the association between group assignment and PSI levels.

11.4 If this study has undergone scientific or scholarly review, please indicate which entity performed the review:

- ☐ Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
- ☐ CTSI Clinical Research Center (CRC) advisory committee
- ☐ Departmental scientific review
- ☑ Other:

Specify **Other**:

NIH: Surgery, Anesthesiology & Trauma (SAT) Study Section

12.0 Background

12.1 Background:

Because of increasing life expectancy and improved anesthesia and surgical techniques in the US, more surgical procedures are being performed on the very old. The older population has the highest rate of surgical procedures. Although many older patients have good perioperative outcomes, postoperative cognitive changes, in particular postoperative delirium, remains one of the most prevalent consequences of surgery. Delirium is an acute confusional state with alterations in attention and consciousness (1), occurring in 10% to 60% of patients after major surgery, with associated mortality rates of 10%-65% (2, 3). In contrast, postoperative cognitive decline (POCD) refers to declines in cognitive functioning that can occur in the absence of delirium, and reported to occur in 7-26% of patients (4-7). POCD has also been associated with impairments in daily functioning (8), premature departure from the labor market (9), and dependency on government economic assistance after hospital discharge (9).

The development of delirium is thought to be a multifactorial process in which there is a complex interrelationship between baseline patient vulnerability and precipitating factors or insults (10). In surgical patients, predisposing risk factors for delirium include age, pre-existent cognitive impairment, and pain, etc. (11, 12). Precipitating factors include events related to surgery such as type of surgery, blood loss, exposure to medications with effects on the central nervous system such as opioids, and sleep disruption, etc. (11-14).

Recently, it has been proposed that deep anesthetic depth contributes to an increased rate of postoperative delirium and POCD. In a study of patients undergoing hip fracture repair receiving a spinal anesthetic, the use of light propofol sedation decreased the prevalence of postoperative delirium by 50% compared with deep sedation (15). A more recent larger study in older patients undergoing non-cardiac surgery reported that intraoperative monitoring with a processed electroencephalogram (EEG) – Bispectral index (BIS), resulted in a reduced rate of postoperative delirium. The investigators further showed that by multivariate analysis, deep anesthesia was independently predictive of postoperative delirium (16), but not POCD. In contrast, other similar studies, which utilized the BIS monitor, did not show that low BIS levels were associated with early POCD. For example the study by Chan et al., reported that BIS-guided anesthesia reduced anesthetic exposure and decreased the risk of POCD at 3 months after surgery but not at one week after surgery (17). This result is curious because if anesthetics were to exert a "toxic" effect on the brain, one would expect to see POCD occurring immediately after surgery and not only at three months after surgery. Two additional smaller studies in fact showed contradictory results, reporting that deeper levels of anesthesia were associated with better postoperative cognitive status (18, 19). Of critical importance is that no previous study had determined the mechanism as to how deep levels of sedation or anesthesia result in postoperative delirium or cognition. As a result, current data on whether deep anesthesia is harmful to the brain are inconclusive.

Furthermore, previous studies addressing anesthetic depth and cognitive outcomes did not consider preoperative cognitive status as a potential moderator for the effects of anesthetic depth on postoperative cognitive outcomes. Specifically, one of the most important baseline patient related factors contributing to adverse postoperative cognitive outcomes is pre-existing cognitive impairment. Studies in patients with Alzheimer's disease and mild cognitive impairment noted that abnormalities of resting state cortical EEG rhythms were not epiphenomena but were related to atrophy of cortical gray matter and cognition (20). Therefore, a numerical value presented on BIS may simply represent a marker of some pre-existent decreased brain or cognitive function, independent of the exposure to anesthetics. Alternatively, the depth of anesthesia may also be a marker for patient's baseline brain vulnerability to the effects of anesthetics.

Recently, some in the anesthesia field advocate that older patients should be routinely monitored by anesthetic depth monitor to avoid deep levels of anesthesia and its potentially adverse effects on

postoperative cognition. The implication that anesthetic is potentially toxic raises a public health concern that has not been thoroughly validated. In fact, population studies suggest otherwise. An exposure to general anesthesia, including frequency and duration of exposure was not predictive of cognitive performance (21). In another study by Avidan et al., the trajectory of cognitive decline on long-term follow up was not affected by prior exposure to an anesthetic (22). Finally, a meta-analysis on the effect of general anesthesia and regional anesthesia on postoperative delirium and POCD also concluded that there was no effect of anesthesia on these two outcomes (23), but this analysis did not consider the effects of anesthetic depth. Taken together, it is timely and critically important to design a study to evaluate the effects of anesthetic depth on cognitive outcomes with proper consideration of patients' baseline cognitive status, and other potential precipitating factors which have been demonstrated in previous studies to be independent factors for postoperative delirium and cognitive decline. Some of these precipitating factors include intraoperative blood transfusion which may incite an inflammatory response (24), intraoperative blood pressure changes (25), and postoperative pain and opioids use, etc. (26).

Accordingly, we aim to determine the feasibility and safety of conducting a randomized control trial with the ultimate goal to measure whether anesthetic depth during surgery contributes to an increased incidence of adverse postoperative cognitive outcomes as measured by delirium or cognitive decline, adjusted for preoperative cognitive function, and other known risk factors.

12.2 Preliminary studies:

The principal investigator has been involved in outcomes research in the older hospitalized patients for over 20 years. Our recent work focuses on understanding the pathophysiology and significance of postoperative delirium. The preliminary studies that are relevant to the aims proposed include:
Burst suppression and postoperative delirium - In a recent pilot study we just conducted (Anesthetic Depth and Postoperative Delirium Trial, 12-12510), we have enrolled 51 patients who underwent non-cardiac surgery at UCSF (May 2nd, 2014 to December 16th, 2014). All patients were monitored with the Sedline brain monitor and postoperative delirium and cognitive status were evaluated. All the raw EEG waveforms were analyzed by two neurologists who were blinded to patient demographics, anesthesia and cognitive outcome data. The Patient State Index (PSI), a continuous processed EEG number which represents anesthetic depth was also continuously recorded.

The major preliminary findings in this pilot study are:
1. Delirium is significantly associated with longer time and larger percent of burst suppression
2. Burst suppression seen on the raw EEG is typically associated with low PSI values (median PSI about 15)
3. Most anesthetized subjects who had no burst suppression have a median PSI value of about 35

Use of a sedation monitor – SEDline brain monitor in older patients - We performed a pilot study of 24 older patients to determine the feasibility of the SEDline brain monitor in monitoring sedation level. In all enrolled subjects, we were able to continuously monitor their EEG and retrieve the raw EEG for review and analysis. The SEDline monitor records not only the sedation level by way of a patient state index (PSI) but also provides 4 channel of raw EEG. As illustrated in figure 1a where the SEDline monitor was applied in one patient who received intravenous sedation, the sedation level as measured by the PSI (green color) fluctuated from high (90) which indicates awake, to deep (50 or below). In contrast, in a second patient (figure 1b) who did not receive sedation initially, the PSI remained relatively unchanged illustrating an awake state.

The importance of including preoperative patient vulnerability factor in delirium studies – We have conducted several cohort studies to examine the impact of possible preoperative patient vulnerability factors in influencing postoperative delirium. We identified that preoperative symptoms of depression (27), preoperative physical frailty (28), and preoperative cognitive status (26) have independent effects on affecting risk of postoperative delirium. These previous studies have provided us with an evidence-based approach to include appropriate variables that may modify the effects of anesthetic depth on postoperative delirium and POCD.

Consideration of moderators in risk modeling – In 581 patients who were prospectively followed for the development of postoperative delirium (26), we first developed a prediction model to determine which patients were at high vs. low risk for the development of delirium based on preoperative risk factors including co-morbidities. We then modeled whether preoperative risk for delirium moderates the effect of postoperative pain and opioids on incident delirium. Compared to patients at low preoperative risk for developing delirium, the relative risk for postoperative delirium in the high preoperative risk group was 2.38 (95% CI = 1.67-3.40). A significant three-way interaction indicates that preoperative risk for delirium significantly moderated the effect of postoperative pain and opioid use on the development of delirium. This study illustrates the importance of moderators in influencing risk models of delirium.

Experience in conducting randomized control trial (RCT) – our group is experienced in conducting large-scale RCT. We have recruited over 700 patients in a study currently funded by the NIH to validate the

results of a pilot study showing that gabapentin as an add-on agent in the treatment of postoperative pain in older patients undergoing spinal surgery reduced postoperative delirium (29). Recruitment of this study is close to completion and we expect results in 3 months.

12.3 References:

1. Lipowski Z. Delirium (acute confusional states). JAMA. 1987;258:1789-92.
2. Lipowski Z. Delirium in the elderly patient. New Engl J Med. 1989;320:578-82.
3. Inouye S. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. Am J Med. 1994;97:278-88.
4. Modena M, Muia N, Sgura F, Molinari R, Castella A, Rossi R. Left atrial size is the major predictor of cardiac death and overall clinical outcome in patients with dilated cardiomyopathy: a long-term follow-up study. Clin Cardiol. 1997;20:553-60.
5. Moller J, Cluitmans P, Rasmussen L, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet. 1998;351:857-61.
6. Johnson T, Monk T, Rasmussen LS, Abildstrom H, Houx P, Korttila K, et al. Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology. 2002;96(6):1351-7.
7. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta anaesthesiologica Scandinavica. 2003;47(3):260-6.
8. Phillips-Bute B, Mathew JP, Blumenthal JA, Grocott HP, Laskowitz DT, Jones RH, et al. Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med. 2006;68(3):369-75. Epub 2006/06/02.
9. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology. 2009;110(3):548-55. Epub 2009/02/20.
10. Inouye S, Charpentier P. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. JAMA. 1996;275:852-7.
11. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. Journal of the American Geriatrics Society. 2006;54(10):1578-89.
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If you have a separate bibliography, attach it to the submission with your other study documents.

13.0 Sample Size and Eligibility

13.1 Number of subjects that will be enrolled at UCSF and affiliated institutions:

204

13.2 Total number of subjects that will be enrolled at all sites (Help Text updated 9/13):

204

13.3 Estimated number of people that you will need to consent and screen here (but not necessarily enroll) to get the needed subjects:

300

13.4 Explain how and why the number of subjects was chosen (Help Text updated 9/13):

Annually, over 1000 patients ≥ 45 years of age undergo major non-cardiac surgery at the University of California, San Francisco Medical Center (2013 operating room data). Therefore, our plan of recruiting 102 patients per year for 2 years is feasible. The sample size calculation is based on an incident postoperative delirium rate of 40% in the three days after surgery (15, 26). We anticipate reduction to 22%, power 0.8, resulting in 102 patients in each group. This sample size is adequate to detect declines in postoperative cognitive functioning across the repeated assessments of cognitive functioning.

13.5 * Eligible age range(s):

- [ ] 0-6 years
- [ ] 7-12 years
- [ ] 13-17 years
- [x] 18+ years

13.6 Inclusion criteria:

≥ 45 years of age
English speaking
Not anticipated to be intubated postoperatively
We will be controlling for the effect of surgery statistically by surgery type.
Postoperative stay of 2 days of more to allow for postoperative cognitive testing

13.7 Exclusion criteria:

Patients who cannot complete the neurocognitive testing including those who will be expected to remain intubated postoperatively.
Patients who are unable to provide informed consent.
Patients who are non-English speaking precluding the administration of neurocognitive tests.
We believe avoiding burst suppression should not be a risk and is not considered light anesthesia per se, however we will exclude patients who may not tolerate light anesthesia - history of untreated hypertension, unstable cerebrovascular disease including stroke, cardiovascular disease including symptomatic heart failure and unstable angina, and patients with a history of intraoperative recall.

13.8 There are inclusion or exclusion criteria based on gender, race or ethnicity:

○ Yes ◉ No

If **yes**, please explain the nature and rationale for the restrictions:

14.0 Drugs and Devices

14.1 * Investigational drugs or biologics will be used OR approved drugs or biologics will be studied under this application:

○ Yes ◉ No

14.2 * Investigational medical devices or in vitro diagnostics will be used OR approved medical devices or in vitro diagnostics will be studied under this application:

◉ Yes ○ No

14.3 * A Non-Significant Risk (NSR) determination is being requested for an investigational device:

○ Yes ◉ No

14.4 Verification of IND/IDE numbers: If the sponsor's protocol does not list the IND/IDE number, you must submit documentation from the sponsor or FDA identifying the IND/IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet.

15.0 Study Device Details

15.1 List the medical devices or in vitro diagnostics to be studied or used and attach any FDA or sponsor correspondence relating to the device to the application in the Study Documents section: (Note: Device category descriptions added to the Help link December, 2014)

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	Sedline Brain Function Monitor	Yes	No	

Manufacturer/Supplier of Device	Masimo Inc.
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	Leung Research Lab: U-368-P
Will Devices be supplied at no Cost	Yes

Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	No
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE Details	The device is being used in accordance with its FDA-approved labeling.
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

16.0 Other Approvals and Registrations

16.1 * Do any study activities take place on patient care units:

(•) Yes ( ) No

If **Yes**, attach a letter of support for the study from the involved patient care manager(s).

16.2 * Does your protocol involve any radiation exposure to patients/subjects? The UCSF Radiation Safety Committee requires review of your protocol if it includes administration of radiation as part of standard of care OR research exposures:

( ) Yes (•) No

16.3 * This study may generate genetic data that may be broadly shared (e.g. submitted to NIH for Genome-Wide Association Studies (GWAS) in dbGaP, TCGA, etc):

( ) Yes (•) No

16.4 * This study involves administration of vaccines produced using recombinant DNA technologies to human subjects:

( ) Yes (•) No

16.5 * This study involves human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to CHR approval):

( ) Yes (•) No

16.6 This study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Radiation Safety Committee

Specify RUA #:

☐ Radioactive Drug Research Committee (RDRC)

Specify RDRC #:

☐ Controlled Substances

17.0 Procedures

17.1 * Procedures/Methods (Help Text updated 9/13) For clinical research list all study procedures, test and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the Methods:

Overview: The incidence and duration of postoperative delirium assessments will be conducted daily for up to 7 days after surgery. For those who stay for more than one week, we will interview them weekly until discharge. Cognitive status also will be measured preoperatively, daily for one week, once weekly for those staying for more than one week. Postoperatively, patients will be contacted 1 month later and 3 months later after surgery for follow-up assessments.

Anesthetic management: the types of anesthetics will not be controlled but will be recorded and analyzed as this is a pragmatic trial. Anesthesiologists will be requested to maintain patients' arterial blood pressure to within 20% of preoperative baseline using vasoactive agents. Patients will receive mechanical ventilation to maintain normocarbia. Intraoperative warming devices will be used to keep body temperature between 36-37 °C. Oxygen saturation will be maintained at >95% throughout surgery. Muscle relaxants will be used during tracheal intubation and only as clinically indicated at other time period during surgery. Patients will be randomized by a random number generation computer into receiving either EEG guided anesthetic depth management vs. standard care. Anesthesiologists caring for patients in the EEG-guided group will keep the PSI >35 to avoid burst suppression. In our prior pilot study, burst suppression occurs in less than 10% of patients when the PSI >35. Anesthesiologists assigned to patients in the standard care group will be blinded to the PSI data. A Sedline monitor will be placed on the patients randomized to receive standard care, but the screen will be covered. As brain monitor is not typically used in standard care of the surgical patients at UCSF, the blinding of the monitoring information is consistent with standard care. In addition to the PSI, we will also record indicators of depth of anesthesia including automatic and somatic responses. Autonomic signs will include heart rate and blood pressure changes, diaphoresis, and lacrimation. Somatic signs will include movement in cases when muscle relaxants will not be used. Explicit recall will be measured. We will measure anesthesiologists' perceived barrier to adhering to the assigned anesthetic depth by a short self-report at the end of each anesthetic. The questions will determine whether the anesthesiologist had difficulty attaining the level of anesthetic depth as specified in the protocol and reasons why they could not, including hemodynamic instability, patient movement, etc.

In the study, we will request that the anesthesia providers to not continue giving paralytic drugs after tracheal intubation unless it is clinically indicated.

In addition, we will monitor and record the use and dosages of all paralytic drugs used during surgery.

Measurement of anesthetic depth: All patients will be continuously monitored before the induction of anesthesia and during surgery with the SEDline Brain Function Monitor (Masimo, Inc., Irvine CA), which provides 4 channels of EEG sampled at 2500 Hz. EEG signals will be filtered and decimated to 250 samples /second with an acquisition bandwidth of 0.5 to 70 Hz. The acquisition montage includes electrodes placed according to the International 10-20 System – Fp1, Fp2, F7, and F8, each referenced to FpZ. EEG data will be stored in a proprietary data format and subsequently converted to the EEG industry standard, European Data Format (EDF). In addition, using proprietary software, a continuous display of the anesthetic depth, known as the patient state index (PSI) will be displayed and recorded continuously. The PSI is a clinically validated measure of the effect of anesthesia and sedation (31). Both the raw EEG data and the PSI data will be stored on computer for analysis. We will analyze PSI by examining the total time that each patient is kept within the prescribed level of anesthetic depth, and the amount of time outside of the assigned range.

Measurement of Cognitive Status: Postoperative cognitive dysfunction will be measured by the digit symbol substitution test (47) the timed verbal fluency test, (48) and the word list learning task (49) in order to assess the cognitive domains of memory and learning (word list), verbal and language skills

(verbal fluency), attention, concentration, and perception (digit symbol test). These tests target domains that are sensitive to drug effects (50) but have been used and validated in a large number of older surgical patients (51).
Alternate forms will be administered at each testing interval, using a Latin-square design. Cognitive assessments will be conducted daily for up to 7 days after surgery. For those who stay for more than one week, we will interview them weekly until discharge. We have successfully collected cognitive data from more than 600 older surgical patients and have described predictors and outcomes of POCD (38) and developed and validated procedures for handling missing data (39). For each test, we will determine whether the patient experienced a significant decline from preoperative baseline using prediction intervals (50). A decline from preoperative performance of 4 or more points for the word list, or 7 or more points for the verbal fluency and the digit symbol tests is considered significant decline and the subject will be classified as having POCD for that day. If decline in performance is observed for at least one postoperative day, we will conclude that POCD occurs for that patient. Prediction intervals consider initial level of functioning, learning effects, and correlations between repeated responses unlike other studies of POCD that rely on determining incidence based on sample norms and not change in the individual's level of performance.
Measurement of Delirium: For the occurrence of delirium, we will use the Confusion Assessment Method Rating Scale (CAM) (40) which was developed as a screening instrument based on operationalization of DSM-III-R criteria for use by nonpsychiatric clinicians in high-risk settings. The postoperative delirium and cognitive assessments will be conducted daily for up to 7 days after surgery. For those who stay for more than one week, we will interview them weekly until discharge by research assistant blinded to the randomization. During the interview, we will check immediate recall of a story and interview a family member or physician/nurse to determine if the patient had experienced an acute change in mental status prior to the preoperative assessment as defined by the CAM. This method has a sensitivity of 94-100% and a specificity of 90-95% and has a high interobserver reliability (40), and have convergent agreement with four other mental status tests. The research assistant will be trained in the use of the CAM until the inter-rater reliability between Dr. Sands and trainee reaches 0.96. That training will be based on a detailed manual developed by Inouye et al. for administration of the CAM (40). For the severity of delirium, we will use the Memorial Delirium Assessment Scale (MDAS) (41) to rate delirium severity.
Other variables associated with incident delirium: We will collect additional variables that have been shown in prior work to be associated with delirium to ensure that our randomization resulted in groups with equivalent predisposition for incident postoperative delirium. The additional variables will include demographic characteristics such as marital status, level of education, living situation, and co-morbidities. Pre- and post-operative pain will be measured by the visual analog scale. Mood will be measured preoperatively using the Geriatric Depression Scale (42). Information on anesthetic agents, doses, anesthetic risk, surgery duration and risk, estimated blood loss, etc. will be obtained by reviewing the anesthesia record. Patients' medical records will be reviewed to obtain the type and daily doses of all opioid analgesics used during the intraoperative period and also daily during the postoperative period until discharge. The type and quantity of all other less commonly used analgesics and all medications with central nervous system effects will also be measured. Intraoperative systolic, mean and diastolic blood pressure and heart rate will be continuously downloaded onto a computer for subsequent analysis. Increases or decreases from each patient's preoperative baseline values and absolute values will be measured using methods previously published by us (25). The use and quantity of vasoactive agents used during surgery will also be measured. The occurrence of other postoperative adverse outcomes will be measured using pre-defined criteria developed by our previous studies (43, 44). Since sleep disturbance has been suggested to increase the risk of delirium in hospitalized elders, we will measure self reported sleep abnormalities using the Pittsburgh Sleep Quality Index (45), a self-administered survey, preoperatively and also daily for the first week after surgery and at discharge.
Postoperative follow-up:
After hospital discharge, patient will be contacted by phone at one month and three months postoperatively for evaluation of their functional status, pain and sleep problems. The cognitive status will be evaluated by Telephone Interview of Cognitive Status, and the symptoms of depression by the Geriatric Depression Scale.

If you have a procedure table, attach it to the submission with your other study documents.

17.2 Interviews, questionnaires, and/or surveys will be administered or focus groups will be conducted:

(•) Yes ( ) No

List any standard instruments used for this study:

Telephone Interview of Cognitive Status (telephone version of Mini Mental status examination)
Geriatric depression scale
Confusion Assessment Method

Neurocognitive tests (Digit Symbol, Word list, Verbal fluency, Digit Span)
Pittsburgh Sleep Quality Index: a self-administered survey, which measures sleep abnormalities.
Brice Scale: Assesses awareness during anesthesia with subsequent explicit recall
Visual Analog Scale

Attach any non-standard instruments at the end of the application.

17.3 Conduct of study procedures or tests off-site by non-UCSF personnel:

○ Yes ◉ No

If yes, explain:

17.4 Sharing of experimental research test results with subjects or their care providers:

○ Yes ◉ No

If yes, explain:

17.5 * Specimen collection for future research and/or specimen repository/bank administration:

◉ Yes ○ No

17.6 Time commitment (per visit and in total):

Cognitive status will be measured preoperatively, daily for one week, and at 6 weeks after surgery. Approx imately 15 minutes on average will be required to complete the neurocognitive testing for each day of testing. Testing will take slightly longer if a patient is confused after surgery. Participation in the study will take a total of about 2.5 hours. Anesthetic depth monitoring will not require any additional time commitment.

17.7 Locations:

Prepare clinic or inpatient ward (preoperative neurocognitive testing)
UCSF Moffitt-Long operating rooms
Orthopaedic Institute Clinic operating rooms

17.8 Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants:

If the studied patients are injured as a result of being in the study, treatment will be available. The costs of such treatment may be covered by the University of California, San Francisco.

18.0 Specimen Collection for Future Research and/or Specimen Repository/Bank Administration

18.1 Specimens are (check all that apply):

☑ Surplus clinical specimens from a diagnostic or therapeutic procedure

☐ Specimens collected for research purposes only
☐ Other

If Other, explain:

Patients who had preoperative laboratory tests relating to their planned surgery would provide consent to have this "to be discarded blood" banked after routine clinical laboraotry testing performed. This left over blood is normally discarded after clinical testing but we propose to preserve the blood for tissue banking.

18.2 Types of specimens:

☑ Blood
☐ Tissue (describe below):
☐ Existing/archival materials (name source below): --
☐ Other (describe below):

Describe and/or name source:

18.3 Consent will be obtained via:

☐ Separate specimen banking consent form
☑ Specimen banking section within a main research study consent form
☐ Surgical consent form with tissue donation brochure

18.4 Specimens will ultimately be stored (check all that apply):

UCSF

☑ UCSF repository/bank being established under this protocol
☐ Existing UCSF specimen repository/bank with CHR approval

Provide the name of the bank and CHR approval number (if not being banked at UCSF under this protocol):

Outside Entity

☐ Cooperative group bank
☐ NIH
☐ Other university
☐ Industry sponsor
☐ Other

Specify to what institution, cooperative group or company specimens will be transferred:

18.5 Direct identifiers will be sent with specimens or shared with other researchers and/or outside entities:

○ Yes
◉ No
○ N/A - Specimens will not be shared with others

If **Yes**, which identifiers will be sent with specimens:

☐ Name

- [ ] Date of birth
- [ ] Social Security number
- [ ] Medical record number
- [ ] Address
- [ ] Phone number
- [ ] Email address
- [ ] Other dates (surgery date, clinic visit dates, etc.)

If **Yes**, provide a justification for sending direct identifiers with the specimens:

19.0 Establishing a Specimen Repository/Bank at UCSF

19.1 The repository/bank is physically located at (list the address and room number for all locations):

San Francisco General Hospital & Trauma Center
1001 Potrero Ave., Room 2M27
San Francisco, CA 94110

19.2 Methods for maintaining confidentiality:

- [ ] Samples are completely de-identified before being added to the bank/repository. There is no way to link the specimens back to the subjects.
- [ ] Samples are coded and researchers are able to link the specimens to specific subjects. However, future recipients will not receive direct identifiers with the specimens.
- [x] Samples are stored with direct identifiers in the repository. However, future recipients will not receive direct identifiers with the specimens.
- [ ] Samples are coded and/or kept with direct identifiers in the repository. The bank/repository may release identifiers with specimens to researchers under special circumstances with prior IRB approval.

Explain under what circumstances identifiers may be released:

19.3 If the repository/bank maintains the identifiers, list the identifiers that will be maintained with the specimens:

- [x] Name
- [x] Date of birth
- [ ] Social Security number
- [x] Medical record number
- [ ] Address
- [ ] Phone number
- [ ] Email address
- [x] Other dates (dates of surgery, visit dates)

19.4 Clinical follow-up data will be linked to specimens:

- (•) Yes
- ( ) No

If **Yes**, provide duration of follow-up or indefinitely:

Till the subject has deceased, for survival analyses.

19.5 There is a formal specimen utilization review process:

- ( ) Yes
- (•) No

If **Yes**, describe the process:

19.6 Specimens banked at UCSF may be made available to (check all that apply):

- [x] UCSF researchers
- [ ] Non-UCSF researchers
- [ ] Industry

20.0 Alternatives

20.1 Study drug or treatment is available off-study:

- ○ Yes
- ○ No
- ◉ Not applicable

20.2 * Is there a standard of care (SOC) or usual care that would be offered to prospective subjects at UCSF (or the study site) if they did not participate:

◉ Yes ○ No

If yes, describe the SOC or usual care that patients would receive if they choose not to participate:

If the patient choose not to participate in the study, usual standard clinical care will be performed with patient's consent. Currently, anesthetic depth monitors such as BIS or SEDline are not being used routinely during surgery. Anesthetic depth is being estimated by patients' hemodynamics, end-tidal anesthetic concentrations, and known pharmacology of other intravenous drugs.

20.3 Describe other alternatives to study participation that are available to prospective subjects:

If the patient chooses not to participate in the study, usual clinical care will be performed with patient's consent. Currently, anesthetic depth monitors such as BIS or SEDline are not being used routinely during surgery. Anesthetic depth is being estimated by patients' hemodynamics, end-tidal anesthetic concentrations, and known pharmacology of other intravenous drugs.

21.0 Risks and Benefits

21.1 * Risks and discomforts:

General anesthetics by themselves are generally safe in healthy individuals. Depending on the co-existent diseases of the patients, there may be individual anesthesia related risks that are inherent to patients undergoing major non-cardiac surgery such as blood loss necessitating intraoperative blood transfusion, and position related injuries, etc. Specific study-related risks pertaining to the randomization of anesthetic depths may include sympathetic activation (increases in blood pressure and/heart rate) which may necessitate treatment with vasoactive medications such as beta adrenergic blocking agents, and/or anti-hypertensive agents; patient recall of intraoperative events; or patient movement during surgery – these events may be more likely to occur in patients randomized to receiving EEG-guided anesthesia management. For patients randomized to receive standard care, there is no known risk other as brain monitor is not routinely used at UCSF during surgery. We will discuss these risks in more details in the data safety monitoring process below.

21.2 Steps taken to minimize risks to subjects:

To minimize potential risks to subjects, we will carefully monitor the recruitment, enrollment and retention of study subjects. We will monitor the occurrences of potential study related outcomes include compliance to the randomization, and safety measurements such as sympathetic activation, hypotension, intraoperative recall, or intraoperative patient movements. The first safety review will take place after the first month or after the first 10% of the subjects are enrolled, whichever will come first. All study end-points will be closely defined to facilitate ease of monitoring. We will exclude subjects with a history of untreated hypertension, unstable cerebrovascular disease including stroke, and cardiovascular disease including symptomatic heart failure and unstable angina, and patients with a history of intraoperative recall. In addition, we will form a data safety monitoring board to consist of individuals not connected to the study. When the study receives funding, the DSMB membership will consist of individuals not related to UCSF.

21.3 Benefits to subjects:

○ Yes ◉ No

If yes, describe:

21.4 Benefits to society:

From a scientific innovation standpoint, our study will provide a mechanistic insight into the possible relationship between anesthetic depth and postoperative cognitive outcomes, in particularly, whether avoiding burst suppression is beneficial has not been previously evaluated.

Another clinical relevance of our approach is that we have substantial prior experience in modeling of the impact of baseline vulnerabilities on perioperative and long-term outcomes. This experience will help us to evaluate whether randomization resulted in groups with equivalent baseline characteristics known to affect postoperative cognitive outcomes. Information learned from our studies will help to inform patients, families, and physicians alike of the short- and long-term impact of surgery given the baseline vulnerabilities.

Because postoperative delirium and cognitive decline are prevalent in the surgical patients and are associated long-term poor outcomes, our study results are critical to understanding how preoperative cognitive status moderates anesthetic depth on postoperative cognitive outcomes. This knowledge is critical for patient informed consent, care management, and development of future interventions to improve the perioperative and post-discharge care of these older patients.

As a result, we believe that the risks involved (loss of privacy as discussed previously, and minor inconvenience from delirium measurements, cognitive testing, and randomization to EEG-guided anesthesia management are reasonable in relation to the importance of the knowledge that is expected to be gained as a result of the study.

21.5 Explain why the risks to subjects are reasonable:

Recently, some in the anesthesia field advocate that older patients should be routinely monitored by anesthetic depth monitor to avoid deep levels of anesthesia and its potentially adverse effects on postoperative cognition. The implication that anesthetic is potentially toxic raises a public health concern that has not been thoroughly validated. Our proposed study will provide essential data to guide a larger randomized clinical trial to determine if avoiding burst suppression (hence much deeper level of anesthesia) will lead to better cognitive outcomes for the older patients after major surgery.

22.0 Data and Safety Monitoring Plan

22.1 Describe the plan for monitoring data and safety (Help Text updated 9/13):

Prior to the study, a safety and data monitoring board (DSMB) will be formed to consist of two physicians and a statistician not involved in the study.

The DSMB will focus on the following:

a. Performance – subject recruitment, retention, and follow-up, flow of data forms, protocol adherence and quality of data.
b. Safety – the magnitude and frequency of adverse events will be measured. See safety review described below.
c. Intervention – we will monitor and assess for intervention effects, this will include the intraoperative hemodynamics, dose of intraoperative anesthetics and medications, intraoperative recall, anesthesiologists ability to follow the prescribed anesthetic protocols, and other pre-defined adverse events.

After the study receives funding from the NIH, an extramural DSMB will be formed, and the membership will be approved by the NIH.

22.2 This study requires a Data and Safety Monitoring Board:

- (●) Yes
- ( ) No or not sure

If **yes**, press **SAVE and CONTINUE** to move to the next section of the application.

22.3 If No, provide rationale:

- ( ) Social/Behavioral research
- ( ) Phase I trial
- ( ) Treatment IND/Compassionate Use Trial
- ( ) Other (explain below)

If **Other,** explain:

23.0 Data and Safety Monitoring Board

23.1 Provide details from the Data and Safety Monitoring Board's charter, including meeting frequency, and affiliations and qualifications of members:

We will form a Data and Safety Monitoring Board (DSMB) to monitor participant safety, data quality, and to evaluate the progress of the study. Once the grant receives funding, we will select up to 5 members to sit on the DSMB. The membership will need to be approved by the NIH funding institute program director. All members of the DSMB will not have a research relationship with the principal investigator or co-investigators, and will be all external to the investigators' institutions. The chair of the DSMB will also serve as a Safety Officer. The membership will consist of a biostatistician and physician-scientists who will be knowledgeable about the question being studied, but not involved in the actual conduct of the study.

23.2 All of the members of the Data and Safety Monitoring Board are independent of the sponsor:

(●) Yes ( ) No

24.0 Confidentiality and Privacy

24.1 Plans for maintaining privacy in the research setting:

The subject's name will not be used in any published report about this study. All data on each study subject will be linked only by the subject's study number. The original data form containing the subject's personal identifier (such as name, birth date, medical record number) relative to the study number will be kept in a locked filing cabinet, inside a double locked room with a keyed entry, and an electronic key entry identifying all personnel who accessed the room.

It is possible that the study may identify someone with a high number of symptoms of depression. If a patient scores higher than a 6 on the Geriatric Depression Scale, they will be asked if they wish for the study to pass along their score to their primary care doctor. If a patient gives permission, the patient's name and score will be shared verbally over the phone to the doctor. If a patient refuses permission to share this information, then no information will be shared for any reason.

24.2 Possible consequences to subjects resulting from a loss of privacy:

Participation in research may involve a loss of privacy, but information about the patient will be handled as confidentially as possible. Patient's name will not be used in any published report about this study.

The patient's personal identifier of name and score on the Geriatric Depression Scale will only be shared to the patient's primary physician and only if the patient gives permission.

24.3 Study data are:

- [ ] Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
- [x] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [ ] Added to the hospital or clinical medical record
- [ ] Created or collected as part of health care
- [ ] Used to make health care decisions
- [x] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained from a foreign country or countries only
- [ ] Obtained from records open to the public
- [ ] Obtained from existing research records
- [ ] None of the above

If **derived from a medical record**, identify source:

APeX

24.4 Identifiers may be included in research records:

(•) Yes ( ) No

If **yes**, check all the identifiers that may be included:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs

- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier

* Required for studies conducted at the VAMC

24.5 Identifiable information might be disclosed as part of study activities:

- (•) Yes ( ) No

If **yes**, indicate to whom identifiable information may be disclosed:

- [ ] The subject's medical record
- [ ] The study sponsor
- [ ] Collaborators
- [ ] The US Food & Drug Administration (FDA)
- [x] Others (specify below)
- [ ] A Foreign Country or Countries (specify below)

If **Others**, specify:

CHR and UCSF

24.6 Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- [ ] Data are stored securely in My Research
- [x] Data are coded; data key is destroyed at end of study
- [x] Data are coded; data key is kept separately and securely
- [x] Data are kept in a locked file cabinet
- [x] Data are kept in a locked office or suite
- [x] Electronic data are protected with a password
- [x] Data are stored on a secure network
- [ ] Data are collected/stored using REDCap or REDCap Survey
- [ ] Data are securely stored in OnCore

24.7 Additional measures to assure confidentiality and protect identifiers from improper use and disclosure, if any:

The subject's name will not be used in any published report about this study. All data on each study subject will be linked only by the subject's study number. The original data form containing the subject's personal identifier (such as name, birth date, medical record number) relative to the study number will be kept in a locked filing cabinet, inside a double locked room with a keyed entry, and an electronic key entry identifying all personnel who accessed the room.

24.8 This study may collect information that State or Federal law requires to be reported to other officials or ethically requires action:

- ( ) Yes (•) No

Explain:

This study will not elicit information on suicidal ideation which thus will not require reporting to officials or ethically requiring action.

24.9 This study will be issued a Certificate of Confidentiality:

○ Yes ◉ No

25.0 Subjects

25.1 Check all types of subjects that may be enrolled:

- [x] Inpatients
- [x] Outpatients
- [ ] Healthy volunteers
- [ ] Staff of UCSF or affiliated institutions

25.2 Additional vulnerable populations:

- [ ] Children
- [ ] Subjects unable to consent for themselves
- [ ] Subjects unable to consent for themselves (emergency setting)
- [ ] Subjects with diminished capacity to consent
- [ ] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners
- [ ] Economically or educationally disadvantaged persons
- [ ] Investigators' staff
- [ ] Students

Explain why it is appropriate to include the types of subjects checked above in this particular study:

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

26.0 Recruitment

26.1 * Methods (check all that apply):

- [x] Study investigators (and/or affiliated nurses or staff) recruit their own patients directly in person or by phone.
- [ ] Study investigators recruit their own patients by letter. Attach the letter for review.
- [ ] Study investigators send a "Dear Doctor" letter to colleagues asking for referrals of eligible patients. If interested, the patient will contact the PI or the PI may directly recruit the patients (with documented permission from the patient). Investigators may give the referring physicians a study information sheet for the patients.
- [ ] Study investigators provide their colleagues with a "Dear Patient" letter describing the study. This letter can be signed by the treating physicians and would inform the patients how to contact the study investigators. The study investigators may not have access to patient names and addresses for mailing
- [ ] Advertisements, notices, and/or media used to recruit subjects. Interested subjects initiate contact with study investigators. Attach ads, notices, or media text for review. In section below, please explain where ads will be posted.

- [x] Study investigators identify prospective subjects through chart review. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [ ] Large-scale epidemiological studies and/or population-based studies: Prospective subjects are identified through a registry or medical records and contacted by someone other than their personal physician. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [ ] Direct contact of potential subjects who have previously given consent to be contacted for participation in research. Clinic or program develops a CHR-approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form for another CHR-approved study.
- [ ] Study investigators list the study on the School of Medicine list of UCSF Clinical Trials website or a similarly managed site. Interested subjects initiate contact with investigators.
- [ ] Study investigators recruit potential subjects who are unknown to them through methods such as snowball sampling, direct approach, use of social networks, and random digit dialing.
- [ ] Other

If **Other**, explain:

26.2 * How, when, and by whom eligibility will be determined:

Eligibility will be determined by chart review (age, type of surgery) by either the principal investigator or the research associates. This will take place typically from one to seven days before the planned surgical procedure.
Inclusion criteria will include that the patient be ≥ 45 years of age, undergoing major non-cardiac surgery for whom general anesthesia can be administered, English speaking, and not anticipated to be intubated postoperatively.

Exclusion criteria will apply when the patient cannot complete the neurocognitive testing including those who will be expected to remain intubated postoperatively, are unable to provide informed consent, are non-English speaking precluding the administration of neurocognitive tests, and may not tolerate light anesthesia - history of untreated hypertension, unstable cerebrovascular disease including stroke, cardiovascular disease including symptomatic heart failure and unstable angina, and patients with a history of intraoperative recall. An additional criterion includes patients with surgical site on the same areas where the SEDline forehead sensors will be placed.

26.3 * How, when, where and by whom potential subjects will be approached:

As stated above, after a review of their medical record to determine the eligibility criteria, potential subjects will be approached by either the principal investigator or one of the trained research assistants in either by phone or the Prepare Clinic (preoperative clinic). This will take place typically from one to seven days before the planned surgical procedure. The study subjects are given as much as time as they wish before signing the informed consent in the preoperative period.

The research assistant will follow the phone script. If the patient is interested in participating, he or she will be required to sign the consent form in person before the surgery and before he or she is officially enrolled in the study. The patient will be sent by mail or email a copy of the information sheet.

26.4 * Protected health information (PHI) will be accessed prior to obtaining consent:

(•) Yes ( ) No

27.0

Waiver of Consent/Authorization for Recruitment Purposes

This section is required when study investigators (and/or affiliated nurses or staff) recruit their own patients directly.

27.1 * Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified:

- (•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

27.2 * A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

27.3 * Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

27.4 * Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

27.5 * Describe any health information that will be collected prior to obtaining informed consent:

Age, type of surgery, primary language, name, date of surgery, eligibility criteria

Note: HIPAA requires that you collect the minimum necessary.

27.6 * Describe your plan to destroy the identifiers at the earliest opportunity consistent with the research or provide a health or research justification for retaining the identifiers, or indicate and explain that retention is required by law:

Patient information will be discarded securely.

28.0 Informed Consent

28.1 * Methods (check all that apply):

- [x] Signed consent will be obtained from subjects and/or parents (if subjects are minors)
- [x] Verbal consent will be obtained from subjects using an information sheet or script
- [ ] Electronic consent will be obtained from subjects via the web or email
- [ ] Implied consent will be obtained via mail, the web or email
- [ ] Signed consent will be obtained from surrogates
- [ ] Emergency waiver of consent is being requested for subjects unable to provide consent
- [ ] Informed consent will not be obtained

28.2 * Process for obtaining informed consent:

As stated above, after a review of their medical record to determine the eligibility criteria, potential subjects will be approached by either the principal investigator or one of the trained research assistants in either by phone /mail, the Prepare Clinic (preoperative clinic) or on the ward if they have been pre-admitted for the planned surgical procedure. This will take place typically from one to seven days before the planned surgical procedure. The study subjects are given as much as time as they wish before signing the informed consent in the preoperative period. Due to changing practice in preoperative evaluation, more than 60% of patients do not come to the hospital for in person evaluation, but by phone only. Therefore, if the patient's case is scheduled as the first case in the morning, in order not to delay the start of surgery, and to still be able to obtain baseline cognitive data, it is more convenient to perform some of the tests on the phone prior to a written consent. For any subjects who have provided verbal consent over the phone, a written informed consent will always be obtained on the day of surgery when the subjects arrive to the hospital, prior to completing the entire preoperative evaluation by the investigators. The preoperative evaluation involves memory tasks, questions about mental and physical health, and health history. This is done in person or over the phone. If the patient is contacted by phone, it will be done by the principal investigator or one of the trained research assistants. For any subjects who have provided verbal consent over the phone, a written informed consent, will always be obtained on the day of surgery when the subjects arrive to the hospital, prior to completing the entire preoperative evaluation by the investigators.

The study subjects are given as much as time as they wish before agreeing verbally to participate. If the patient is interested in participating, the researcher will document the patient's verbal consent and the patient will be required to sign the consent form in person before the surgery. A copy of the infomation sheet will be made available to individuals providing verbal consent. Depending on the patient's preference, the consent form will either be air mailed or electronically mailed to the patient. The preoperative evaluation will be done over the phone or in person, before or after the patient's visit to the preoperative clinic, depending on the patient's availability. Thus, the preoperative evaluation (memory tasks, questions about mental and physical health, and health history) will be done occasionally before the investigator meets with the patient in person and before written consent is ultimately obtained. A written cognitive test that takes 2 minutes will be done always in person after written consent is obtained.

28.3 * How investigators will make sure subjects understand the information provided to them:

The Principal Investigator has been conducting patient related research for over 20 years at UCSF. At the time of consenting, we always ask the potential study subjects if they understand the research study and if they have any questions before signing the informed consent. Also, a consent form is given to them and all the items reviewed systematically with each potential subject.

29.0 Waiver of Signed Consent (Verbal/Electronic Consent)

29.1 * Select the regulatory category under which the CHR may waive the requirement to obtain *signed* consent:

- ○ 46.117(c) (1) The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern
- ◉ 46.117(c) (2) The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context

30.0 Financial Considerations

30.1 Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- ☑ Subjects will not be paid
- ☐ Cash
- ☐ Check
- ☐ Debit card
- ☐ Gift card
- ☐ Reimbursement for parking and other expenses
- ☐ Other:

Specify **Other**:

30.2 Describe the schedule and amounts of payments, including the total subjects can receive for completing the study. If deviating from recommendations in Subject Payment Guidelines, include specific justification below.

30.3 Costs to Subjects: Will subjects or their insurance be charged for any study procedures?

◉ Yes ○ No

If **yes,** describe those costs below, and compare subjects' costs to the costs associated with alternative care off-study. Finally, explain why it is appropriate to charge those costs to the subjects.

Subjects or their insurance will only be charged for standard care for the cost of anesthesia. This is done as part of clinical routine practice.
Subjects wil not be billed for monitoring from the SEDline device.

31.0

CTSI Screening Questions

31.1 * **This study will be carried out at one of the UCSF Clinical Research Services (CRS) centers or will utilize CRS services. CRS centers are at the following sites:**

- **SFGH Clinical Research Center**
- **Moffitt Adult Clinical Research Center**
- **Moffitt Hospital Pediatrics & NCRC**
- **Mount Zion Hospital Clinical Research Center**
- **Tenderloin Center**
- **CHORI Children's Hospital Pediatrics & Adult Clinical Research Center**
- **Kaiser Oakland Research Unit**
- **SF VA Medical Center Clinical Research Unit**

Please note: Effective 3/1/14, the CRS form will no longer be completed and submitted in iRIS. The CRS budget request form can be found at: https://accelerate.ucsf.edu/files/crs/BudgetRequest2015.docx. Follow the instructions on the form to submit. Even if you click 'Yes' to this question, the form will no longer proceed to the Clinical Research Services (CRS) Application Form section.

○ Yes ◉ No

31.2 This project involves community-based research:

○ Yes ◉ No

31.3 This project involves practice-based research:

○ Yes ◉ No

32.0 End of Study Application

32.1 **End of Study Application Form** **To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.**

University of California
San Francisco

Human Research Protection Program
Institutional Review Board (IRB)

Expedited Review Approval

Principal Investigator
Dr. Jacqueline M Leung, MD, MPH

Type of Submission: Continuing Review Submission Form
Study Title: The Effect of Anesthetic Depth on Postoperative Cognitive Outcomes, II

IRB #: 14-14273
Reference #: 227548
Committee of Record: Laurel Heights Panel
Study Risk Assignment: Greater than minimal

Approval Date: 07/25/2018 **Expiration Date:** 07/24/2019

Regulatory Determinations Pertaining to this Approval:

This submission was eligible for expedited review as:
Category 8(c): Renewal of inactive research protocols or protocols that are essentially complete: where the remaining research activities are limited to data analysis

IRB Comments:

All changes to a study must receive UCSF IRB approval before they are implemented. Follow the modification request instructions. The only exception to the requirement for prior UCSF IRB review and approval is when the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103.b.4, 21 CFR 56.108.a). In such cases, report the actions taken by following these instructions.

Expiration Notice: The iRIS system will generate an email notification eight weeks prior to the expiration of this study's approval. However, it is your responsibility to ensure that an application for continuing review approval has been submitted by the required time. In addition, you are required to submit a study closeout report at the completion of the project.

For a list of all currently approved documents, follow these steps: Go to My Studies and open the study – Click on Informed Consent to obtain a list of approved consent documents and Other Study Documents for a list of other approved documents.

San Francisco Veterans Affairs Medical Center (SFVAMC): If the SFVAMC is engaged in this research, you must secure approval of the VA Research & Development Committee in addition to UCSF IRB approval and follow all applicable VA and other federal requirements. The UCSF IRB website has more information.