1. Title

A Strategy to Reduce the Incidence of Post-Operative Delirium in Elderly patients (The STRIDE Study)

2. Trial registration

STRIDE is registered at ClinicalTrials.gov under registration number: NCT00590707.

3. Protocol version

Version 12, last revised on November 19, 2012

4. Funding:

The National Institute of Aging (NIA), National Institutes of Health, United States funds STRIDE under Grant R01 AG033615, Principal Investigator (PI): Frederick E. Sieber. The PI does not have any financial or competing interests to report.

5. Roles and responsibilities

5a. Names, affiliations, and roles of protocol contributors:

Role	Name	Contact
Intervention		
Principal Investigator	Frederick E. Sieber, MD	410-550-0942 fsieber1@jhmi.edu
Study Anesthesiologist	Jean-Paul Ouanes, DO	410-550-4987 ouanes@jhmi.edu
Study Anesthesiologist	Mahmood Jaberi, MD	410-550-1389 mjaberi3@jhmi.edu
Study Surgeon	Erik Hasenboehler, MD	410-955-1796 ehasenb1@jhmi.edu
Trial oversight, coordination, and data management		
Trial Oversight and Coordination	George Bigelow PhD	410-550-0035 bigelow@jhmi.edu
Assessment		
Project Coordinator; Recruitment & Interview Team	Kori Kindbom, MA	410-550-0984 kindbom@jhmi.edu
Recruitment & Interview Team	Michael Sklar, MA	410-550-1542 msklar1@jhmi.edu
Recruitment & Interview Team	Rachel Burns	410-550-1704 rschepis@jhmi.edu
Study Psychiatrist Director of Delirium Assessment and Delirium Consensus Panel	Karin Neufeld, MD	410-502-1169 kneufel2@jhmi.edu
Study Psychiatrist Delirium Consensus Panel member	Paul Rosenberg, MD	410-550-9883 prosenb9@jhmi.edu
Study Geriatrician Delirium Consensus Panel member	Esther Oh, MD	410-550-1318 eoh9@jhmi.edu
Study Design		
Clinical Trialist*	Kay Dickersin, MA, PhD	410-502-4421 kdicker3@jhu.edu
Clinical Trialist*	Tianjing Li, MD, MHS, PHD	410-502-4630 tli19@jhu.edu
Epidemiologist*	L. Susan Wieland, MPH, PhD	swieland@som.maryland.edu
Study Biostatistician	Nae-Yuh Wang, PhD	410-955-3700 naeyuh@jhmi.edu

Data Safety Monitoring Board		
Chair	Jeffery Carson, M.D.	732-235-7122 carson@umdnj.edu
Medical Safety Officer	Sarang Kim, MD, FACP	732-235-7253 kimsa@umdnj.edu
Anesthesiologist	Lee Fleisher, M.D.	215-662-3776 lee.fleisher@uphs.upenn.edu
Psychiatry	Steve Epstein, M.D.	202-784-0682 epsteins@gunet.georgetown
Epidemiologist	Jay Magaziner, PhD	jmagazin@epi.umaryland.edu
Biostatistician	Anne Lindblad, PhD	alindblad@emmes.com

* Worked on the design of the trial in Year 01.

5b. Name and contact information for the trial sponsor

NIA program officer:
Molly Wagster
301-496-9350
wagsterm@nia.nih.gov

5c. Role of study sponsor and funder

The program officer or other representative of the NIA attends open session of the Data and Safety Monitoring Board (DSMB) meetings. The study sponsor (i.e., NIA) has no other roles in study design; collection, management, and interpretation of data; writing of the report; or the decision to submit the report for publication.

5d. Composition, roles, and responsibilities of the individuals overseeing the trial

The Study management structure comprises two standing committees: the STRIDE Investigators Executive Committee and the DSMB. Study operations are carried out under the direction of the STRIDE Investigators Executive Committee, which is comprised of the PI and respective individuals supervising cognitive assessments (KN), data management/data analysis (NYW), and clinical trial oversight (GB).

The responsibilities of the STRIDE Investigators Executive Committee include:

- Review and approve the procedures for the conduct of the study, including: recruitment and treatment procedures, data collection procedures and forms, data management and analysis procedures, and the Manual of Procedures (MOP);
- Approve major changes in the above;
- Set priorities;
- Review study progress (including recruitment) and take action to correct deficiencies;
- Resolve technical issues that arise during the execution of the trial;
- Resolve operational problems brought to the committee by members of the STRIDE staff
- Take action on advice from the DSMB concerning the continuation and conduct of the trial, including recommendations concerning premature termination because of evidence of harmful or beneficial results;
- Ensure confidentiality of participant data;
- Review and approve ancillary studies, and provide oversight for publication of study findings.

The PI of STRIDE is responsible for clinical oversight of the trial. Specific duties include:

- Organize and conduct training sessions for physicians;
- Advise and oversee clinical aspects of the study protocol and data collection;
- Resolve all technical questions with regard to treatment and complications;

- Survey the published literature on use of light sedation for hip fracture surgery in the elderly in an ongoing fashion and report any critical information promptly to the STRIDE Investigators Executive Committee;
- Communicate with both intervention and assessment personnel regarding recruitment and other issues;
- Provide representation to the STRIDE Investigators Executive Committee and DSMB;
- Ensure confidentiality of patient data;
- Assist with development of study documents, including data collection forms, MOP, and study reports;
- Prepare and distribute minutes of STRIDE Investigators Executive Committee;
- Prepare all necessary reports for NIA and study committees;
- Collaborate and take a leadership role in the preparation of scientific reports for publication;
- Provide arrangements for all committee meetings, including the STRIDE Investigators Executive Committee and DSMB meetings;
- Manage financial contracts; and
- Provide reimbursement to STRIDE staff for pre-approved study travel.
- Ensure that masking is maintained throughout study.

The responsibilities of Trial Oversight and Coordination are:

- Provide scientific expertise in the design and operation of STRIDE;
- Provide representation to the STRIDE Investigators Executive Committee and the DSMB;
- Prepare, maintain, and distribute study documents such as the MOP and forms;
- Provide facilities and staff to carry out analyses designed to monitor performance of the STRIDE clinical center, including patient recruitment and eligibility;
- Supervise and monitor performance of STRIDE data collection, processing, and analysis procedures;
- Prepare analyses of study data, including interim analyses for the DSMB and study monitoring;
- Ensure confidentiality of participant data;
- Respond to day-to-day clinical center needs regarding data collection and protocol administration;
- Collaborate and take a leadership role in the preparation of scientific reports for publication.
- Prepare and distribute meeting minutes for the DSMB;
- Serve as the official STRIDE archive;
- Develop and maintain a storage system for all study documents;
- Develop and implement a data storage system with security and backup features for all study data;
- Prepare all necessary adverse events reports for the NIA, Institutional Review Board (IRB), and DSMB.
- Prepare training materials related to the study;
- Train clinical center staff in study methods and procedures related to data collection and procedures designed to minimize bias;
- Coordinate certification of clinical center and study staff
- Develop and implement quality assurance and control monitoring programs.

Data Management responsibilities include:

- Design and development of all data systems related to the study;
- Software training related to data entry and software system use;
- Maintain computerized master file of edited study data
- Maintain audit trail of all study data.
- Generate patient randomization assignments and oversee the system for central randomization;
- Generate patient emergency randomization envelopes for the Study Anesthesiologist/Anesthetist to use as backup to the electronic system;
- Provide facilities and staff to assist Study Biostatistician carrying out analyses designed to monitor performance of the STRIDE clinical center, including patient recruitment and eligibility;
- Provide facilities and staff to assist Study Statistician preparing frozen data sets for interim analyses for the DSMB and other study monitoring, as well as analyses for publication; and

- Collaborate in the preparation of scientific reports for publication.
- Provide and support a data storage system with security and backup features for all study data; and
- Collaborate, as needed, in the preparation of all necessary reports for the NIA and study committees.

The Intervention Team has the following responsibilities:

- Complete appropriate forms on all potentially eligible patients screened for participation;
- Verify the pre-randomization eligibility of all patients enrolling in the trial, including the patient's willingness to accept the randomized treatment assignment;
- Perform randomization procedures for patients eligible and willing to participate in the randomized trial;
- Make the necessary preparations for providing the assigned treatment;
- Treat patients according to the randomized assignment;
- Maintain masking of patient's treatment assignment.

The Assessment Team is composed of the Recruitment & Interview Team and the Delirium Consensus Panel. The Recruitment & Interview Team has the following responsibilities:

- Attend ongoing STRIDE sessions on quality assurance, training, certification, and recertification of personnel;
- Undergo certification and recertification procedures designed to maintain the quality of study activities;
- Complete, enter and submit copies of data collection forms in an accurate and timely fashion;
- Maintain a roster and complete forms on all potentially eligible patients screened for participation;
- Verify the pre-randomization eligibility of all patients enrolling in the trial, including the patient's willingness to accept the randomized treatment assignment;
- Carry out the patient education and consent process;
- Follow the recruited patients using prescribed STRIDE follow-up procedures;
- Ensure confidentiality of patient data; and
- Provide input during consensus panel meetings.

The Assessment Team leader has the following responsibilities:

- Train research staff in administration of the delirium and dementia assessment instruments, including
  - Mini Mental State Examination (MMSE);
  - Confusion Assessment Method (CAM);
  - Delirium Rating Scale, Revised, 1998 (DRS-R-98);
  - Clinical Dementia Rating (CDR);
  - Mini-Mental State Exam (MMSE);
  - Abbreviated Digit Span Test (DST); and
  - Geriatric Depression Scale (GDS).
- Conduct quality assurance for CAM and DRS-R-98 ratings;

Responsibilities of the Delirium Consensus Panel includes:

- Review all participant delirium testing and finalize participant delirium outcome classification and ascertainment.

5e. Study team eligibility

STRIDE certification is required for intervention and Assessment Team members. All study personnel requesting certification must attend training sessions conducted by the STRIDE Investigators Executive Committee. The training will include information about the study protocol, procedures, form completion, and data entry, as well as basic concepts of research and bioethics.

All study personnel requesting certification must read the MOP, review data collection forms, complete the Knowledge Assessment Test, and read and sign the Commitment to Maintain Study Masking. All study personnel must complete the Human Subjects Research and the Health Insurance Portability and

Accountability Act (HIPAA) certification courses as required by the local IRB and submit the certification of completion to the Johns Hopkins IRB.

Certification requirements for personnel taking on a specific role are summarized in the MOP. In brief, intervention team members must be able to provide spinal anesthesia using STRIDE protocol; Assessment Team members must be trained to administer standardized psychiatric and functional measurements and be trained to complete study forms. Trial Oversight and Coordination is responsible for implementation and maintenance of all certification procedures. All certification documentation is submitted to Trial Oversight and Coordination, who is responsible for recommending and documenting certification.

6. Introduction

6a. Background and rationale

The incidence of delirium in elderly patients after major elective surgery has been estimated at 10%, but appears to be higher following cardiac surgery and hip fracture repair[1]. Incident delirium is an important predictor of longer hospital stay and increased health costs[2]. Overall, 2-3 million elderly patients per year sustain delirium during their hospital stay, involving more than 17.5 million inpatient days and accounting for more than $4 billion in Medicare expenditures[3].

The mainstay of delirium management is prevention by control and/or elimination of modifiable risk factors. One such risk factor may be sedative medications, where both drug selection and dosage can be modified. The role of sedative medications as iatrogenic risk factors for delirium has been described in ICU patients[4]. It seems logical that the management of intraoperative sedation would be an important modifiable risk factor to target; however, little work has been done in this area.

6b. Explanation for choice of comparator

The question of whether light vs. deep sedation can decrease the risk of postoperative delirium was examined in a recent randomized double masked trial[5]. Briefly, 114 hip fracture patients underwent spinal anesthesia with propofol sedation. Level of sedation was assessed by monitoring the Bispectral index (BIS). Patients were randomized to one of two intraoperative sedation levels: Light sedation was defined by a BIS $\geq$80. Heavy sedation was defined by a BIS of approximately 50. Randomization was stratified by MMSE score and age. Patients were assessed daily for postoperative delirium in hospital using CAM and MMSE. The study demonstrated that in this high risk population, light sedation decreased the prevalence of postoperative delirium on postoperative days 2-5 by 50% compared with heavy sedation (19% in light sedation group versus 40% in the heavy sedation group). The effect was associated with a mean reduction of almost one day of delirium for the light sedation group. This study points to the role of excessive sedation during the perioperative period as a risk factor for delirium in highly vulnerable populations.

Patients in the above-mentioned trial were followed for up to 3 years postoperatively for mortality. Mortality in subgroups of participants with and without postoperative delirium and subgroups of participants receiving light versus deep sedation were compared using Kaplan-Meier analysis. Patients sustaining postoperative delirium had a higher mortality rate than those without delirium (p=0.036, Cox-Mantel). There was a trend towards higher mortality in patients undergoing deep sedation, but this trend did not reach significance (p=0.485), as the sample size and duration of follow-up were inadequate to determine this outcome with certainty.

7. Objective

The principal objective is to assess the effectiveness of light versus heavy sedation during surgery in elderly patients undergoing hip fracture repair.

8. Trial design

STRIDE is a randomized, two-group, parallel, superiority trial. The primary outcome is the impact of the intervention on the incidence of delirium during postoperative Day 1 to Day 5 or to hospital discharge, whichever occurs first. The secondary outcomes are mortality at one year (12 months) after surgery, delirium at 1-month (30 days), and in-hospital delirium at 1-5 days stratified by baseline co-morbidities.

Other outcomes include (1) change in functional outcomes from pre-operative test to 1-month and 12-month follow-up: activities of daily living (ADL) and instrumental ADL (IADL); grip strength; timed chair rise; and timed 3-meter walk; and (2) change in clinical dementia rating between the pre-operative test and 12-month follow-up.

The specific aims of the study as a whole are to:

- Develop and maintain a study team for the purpose of performing the randomized trial;
- Enroll eligible patients at JHBMC;
- Collect data on patients before, during, and after treatment using a standard set of procedures and forms;
- Assemble data for the comparison of the randomized treatment groups;
- Perform analyses of randomized patients to assess the effect of light sedation compared with heavy sedation on patient postoperative delirium;
- Perform analyses to assess the effect of treatment on secondary and other outcomes.

9. Study setting

STRIDE is conducted at a single clinical center (i.e., JHBMC), a tertiary care hospital.

10. Recruitment

All patients posted for traumatic hip fracture surgery at JHBMC are reviewed by a member of the intervention team for potential eligibility for STRIDE. Potentially eligible participants are screened and interviewed by a recruitment & intervention team member concerning choice of anesthesia. Family members or other legally authorized caregivers may also be interviewed as necessary. If the patient chooses spinal anesthesia then a member of the recruitment/interview team will interview and screen the potential subject.

11. Eligibility criteria

Inclusion criteria:

- Admitted to JHBMC;
- Posted to the operating room schedule for traumatic hip fracture surgery, that is a surgery to repair a fracture of femoral neck, intratrochanteric or subtrochanteric as the result of trauma;
- Is 65 years of age or older;
- Speaks and understands English sufficiently well to answer questions related to STRIDE (and reads English at least at a 5th grade level).

Exclusion criteria:

Participant has the following type of fracture/condition:

- Hip fracture that is not a result of trauma;
- Hip fractures in both hips on this admission, as determined by x ray;
- Non-hip fracture (e.g., vertebral fracture, humerus fracture) that will be surgically repaired at the same time as the hip fracture; or
- Prior hip surgery within 5 years on the same hip as the one to be operated on.

Participant had the following types of prescriptions

- Clopidogrel 7 days prior to surgery (or based on clinical judgment using information provided by the participant and the participant's family or caregiver that the participant took Clopidogrel 7 days prior to surgery);
- Ticlopidine within 14 days prior to surgery (or based on clinical judgment using information provided by the participant and the participant's family or caregiver that the participant took Ticlopidine within 14 days prior to surgery);
- Glycoprotein IIB/IIIa inhibitors (or based on clinical judgment using information provided by the participant and the participant's family or caregiver that the participant took glycoprotein IIB/IIIa inhibitors within 48 hours prior to surgery); or

- Fonduparinux within 48 hours prior to surgery (or based on best clinical judgment using information provided by the participant and the participant's family or caregiver that the participant took Fonduparinux within 48 hours prior to surgery).

Participant has the following medical history/current medical condition:

- Very severe chronic obstructive pulmonary disease per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Executive Summary Statement as follows:
  1.Post-bronchodilator FEV1< 30% predicted or FEV1<50% predicted plus chronic respiratory failure. Chronic respiratory failure is defined as PaO2 < 60 mm Hg with or without PaCO2 > 50 mm Hg while breathing air at sea level.
  2.Post-bronchodilator FEV1/FVC <0.70;
- Stage IV heart failure by The New York Heart Association Functional Classification;
- Requires ventilation and intubation at the time of surgery;

Participant has the following lab test results:

- International Normalized Ratio test value ≥1.4;
- Aortic stenosis, defined by the American Society of Regional Anesthesia as both an aortic valve area <0.8 cm^2 AND a mean aortic gradient of >50mm Hg;

Participant has the following scores (mental status criteria):

- MMSE <15;
- A delirium diagnosis at baseline;

12. Interventions

After enrollment and satisfactory administration of spinal anesthesia, the patient will be assigned to one of two groups at random. Randomization will be performed by a web-based system constructed by the ICTR at the JHBMC under the supervision of Dr. Kerry Stewart, in conjunction with the study's biostatistician, Dr. Nae-Yuh Wang. Patients in both groups will receive the institutional standard of care pre-operatively (the preoperative analgesic regimens typically consist of intravenous opioids of either morphione or dilaudid).

Intra-operatively, however, one group will have the depth of sedation (as measured by the use of the Observer's Assessment of Awareness / Sedation Scale [OAA/S]; see Table 1) maintained at an OAA/S score of 0-2. This will be the deep sedation group. Patients in the other group will have the depth of sedation maintained at an OAA/S score of 3-5. This will be the light sedation group. The propofol is titrated individually for each participant to achieve and maintain the depth of sedation required by that participant's assigned treatment group (light or heavy sedation). The depth of sedation for all participants is measured by the OAAS, administered every 15 minutes intra-operatively. Data on amount of propofol and OAAS score are recorded on the Intraoperative Data Form (Form 15). Summary information about anesthesia, pain, surgical times, and receipt of opioids during surgery and PACU stay is collected on the Anesthesia Data /PACU Summary Form (Form 16). Forms 15 and 16 must be stored separately from all other forms by the principal investigator, to maintain the masking of the treatment assignment.

When the Study Anesthesiologist/Anesthetist determines the sedation level of a participant randomized to heavy sedation to be too light (an OAA/S score of 3 or greater), the infusion rate of propofol is increased by 10-20 mcg per kg per minute, and the sedation is reassessed 5 minutes later following the change in infusion rate. This sequence is repeated until a sedation level of 0-2 is obtained. Likewise, when the Study Anesthesiologist/Anesthetist determines the sedation level of a participant randomized to light sedation to be too heavy (an OAA/S score of less than 3), the propofol infusion rate is decreased in steps of 10-20 mcg per kg per minute at a time, with a 5-minute interval before repeating the sequence until an OAA/S score of 3 or greater is achieved.

At the completion of the case, the intervention team member should obtain a printout from the anesthesia monitor in 5-minute intervals which include the following information: systolic and mean blood pressure, and bispectral index (BIS) values.

Problems with sedation protocol:
Too little sedation

- an awake participant requesting more sedation; or
- an agitated participant.

Protocol: The infusion rate of propofol is increased by 10-20 mcg per kg per minute, and the sedation is reassessed 5 minutes later following the change in infusion rate. This sequence is repeated until the patient is comfortable or agitation subsides.

Too much sedation,

- inability of the participant to maintain an airway

Protocol: Placement of an oral or nasal airway is performed and the case is continued.

- hypotension

Protocol: The initial treatment regimen includes a neosynephrine infusion titrated to obtain the desired blood pressure level. Other second-line drugs may include glycopyrrolate, ephedrine, or epinephrine, depending on the clinical circumstances. If the fall in systolic blood pressure persists despite these interventions, then the level of sedation is decreased by decreasing the dosage of the propofol infusion while continuing to manage the blood pressure accordingly.

If a participant does not complete the surgical and anesthesia protocol for any reason, or there is a deviation from the protocol, postoperative data are nevertheless collected. The Protocol Deviation Log (Form 50) will be used to document all information on protocol deviations, including deviations in administration of the study treatment. Clinical trial oversight will tabulate these protocol deviations to the DSMB in a tabulated report.

13. Outcomes

The primary outcome is the impact of the intervention on the incidence of delirium during post-operative Day 1 to Day 5 or to hospital discharge, whichever occurred first. We will evaluate delirium using validated instruments including the CAM, MMSE, Abbreviated DST, and DRS-R-98, followed by case-by-case diagnostic adjudication by the Delirium Consensus Panel. All delirium measurements are taken by a member of the Recruitment & Interview Team. Both the Delirium Consensus Panel and the Recruitment & Interview Team are masked to the treatment assignment.

A clinician qualifies to be on the Delirium Consensus Panel if they are a neurologist, psychiatrist, psychologist, or geriatrician with previous clinical experience in evaluating or managing delirium and the related research tools for its study. The quorum for the Delirium Consensus Panel should consist of a vote by all panel members. The Assessment Team leader will moderate the meeting.

To ensure the validity and consistency of delirium assessment, delirium consensus is performed on all in-hospital delirium assessments as well as the 1-month follow-up assessment on all study participants. Delirium Consensus Panel Members convene and make delirium diagnostic adjudication so that all in-hospital data and 1-month follow-up assessment can be analyzed at once.

Delirium data are always presented in the same structured format. Following presentation of the data, the respective Recruitment & Interview Team members should be available to answer questions concerning their observations.

Postoperative delirium will be defined in this study by criterion for delirium presented in the Diagnostic and Statistical Manual for Mental Disorders, 4th Edition as assessed on the CAM. Based on the CAM algorithm, the Delirium Consensus Panel will assign one of three possible ratings: No delirium, no criteria met; No delirium, but 1 or 2 criteria met; and Delirium, all 3 criteria met. Each voting member will vote to assign each hospital day or 1-month assessment. The majority vote will be considered the diagnosis and will be recorded on the Delirium Consensus Diagnosis Form (In-Hospital Visits) (Form 29A, Form 29A Supplement-DSMIV) and the Delirium Consensus Diagnosis Form (1-Month Follow-up Visits) (Form 29B,

Form 29B supplement-DSMIV).

14. Sample size and power calculation

Based upon a feasibility estimate of 4-year recruitment in a single center setting, sample size is expected to be 200 participants randomized in equal allocation into the two study groups. We expect full outcome observation for in-hospital delirium and 1-year mortality. A total of 176 participants are expected to complete 1-month follow-up, and the expected number for loss to follow-up at this study time point includes participants who die during the follow-up period.

STRIDE is designed to test the primary hypothesis that limiting sedation will lead to a lower risk of postoperative delirium in-hospital. Power evaluation was conducted through calculating the minimal detectable difference between the two treatment arms with 80% power for a 2-sided test based upon expected sample size of 200 and parameter estimates from pilot data obtained from the preliminary trial. Statistical power for the study was evaluated using PASS 2005.

We also evaluated minimal detectable difference for 1-year mortality between the two treatment arms for the main secondary hypothesis that limiting sedation will lead to a lower mortality over the next 12 months. Multiple comparison adjustment was not performed for these evaluations.

14a. Power to test in hospital risk of postoperative delirium

We used data from the preliminary study[5] and the feasible total sample size of 200 within the study time frame to calculate the minimal detectable difference between the 2 treatment arms, as follows. In the preliminary randomized controlled trial[5], there was a 55.6% decrease in postoperative delirium with light sedation. Assuming the risk of postoperative delirium in hospital for the deep sedation group as 39.6%, with a 2-sided alpha of 0.05 using the Fisher's exact test, we will have 80% power to detect an in hospital postoperative delirium rate of 18.5% or lower in the light sedation group, or a 53.3.0% reduction or more on the risk of postoperative delirium in the light sedation group compared to the risk in the deep sedation group. This is based on a sample size of 80 participants per group. Since we anticipate complete follow-up on the primary outcome, i.e. with 100 participants per group, we will be able to detect a postoperative delirium rate of 20.6% or lower in the light sedation group, or a 48.0% reduction or more on the risk of postoperative delirium in the light sedation group compared to the risk in the heavy sedation.

14b. Power to test rate of mortality

In the preliminary study[5], the Kaplan Meier estimate for 1-year mortality was 31.5% for the deep sedation group, and 17.3% for the light sedation group. Assuming the risk of 1-year mortality of 31.5% for the deep sedation group and proportional hazards, we will have 80% power to detect the 1-year mortality rate of 14.4% or lower, or a 17.1% or more absolute reduction in mortality, in the light sedation group. This is based on as sample size of 80 per group with a 2-sided alpha of 0.05 for a log rank test assuming proportional hazards. With a sample size of 100 per group and a 2-sided alpha of 0.05, we will have 80% power to detect a 1-year mortality rate of 16.0% or lower, or a 15.5% or more absolute reduction in mortality, in the light sedation group. We anticipate complete follow-up on mortality outcome at 1-year post randomization.

15. Randomization

15a. Sequence generation

In STRIDE, participants are randomized to either light or heavy sedation in a 1:1 ratio, i.e., the participant has an equal probability of assignment to either group. Randomization is stratified by dementia at baseline (MMSE score 15-23 versus MMSE score 24-30) and participant age (65-79 years versus 80+ years). Dementia and age are baseline factors strongly and consistently associated with postoperative delirium. The Study Statistician generates the random sequence using a computer program.

15b. Allocation concealment and implementation

After baseline data is obtained, a member of the Recruitment & Interview Team enters eligibility data into the tracker/randomization website. After determining whether spinal anesthesia is possible, the Study Anesthesiologist/Anesthetist logs into the Randomization Database in the operating room using his or her Johns Hopkins (JHED) ID and enters the participant ID number into the Randomization Database. The

Randomization Database verifies eligibility and participant ID against existing participant ID numbers in the Randomization Database to prevent duplicate requests of assignment for the same participant ID.

An emergency backup system is also provided for the unlikely possibility that the Randomization Database is completely inaccessible. The backup system is a set of numbered envelopes kept in four boxes for each of the four possible stratification groupings. These boxes of envelopes are stored in the PI's office. The intervention team member selects the box appropriate to the participant's age and MMSE score, then chooses the lowest envelope number available in that box (which should be the first envelope in the box). S/he checks off the envelope number on the front of the box, indicating the envelope has now been used and completes Section C on the front of the envelope and the enclosed Form 70. S/he places Form 70 in the envelope, seals it, and returns it to the data management team.

All participants receive spinal anesthesia. Every attempt should be made to provide spinal anesthesia using propofol only. In most hip fracture patients, spinal anesthesia can be performed following a propofol bolus as needed of 10-50 mg. After enrollment and satisfactory administration of spinal anesthesia, the patient will be assigned to one of two groups at random; randomization will be performed by a web-based system constructed by the Institute for Clinical and Translational Research at JHBMC under the supervision of Dr. Kerry Stewart, in conjunction with the study's biostatistician, Dr. Nae-Yuh Wang.

16. Masking

It is not practical to attempt intra-operative blinding of the intervention team in this study. With the exception of the Study Biostatistician and the Study Anesthesiologist/Anesthetist, all STRIDE team members -- including those assessing study outcomes, those treating the participant, and the participant and participant's family and caregivers -- will be masked as to treatment assignment until data have been analyzed and results reported. All data gathering and delirium/cognitive assessments will be performed by members of the STRIDE team who are masked to the participant's intraoperative level of sedation assignment. Masked study investigators must refrain from making any attempt to learn of a participant's anesthesia level (either assigned or received), which would result in the unmasking of the participant's treatment assignment.

At the clinical center, only the Study Anesthesiologist/Anesthetist is unmasked, and is unmasked only in the case of his or her patients. The Study Anesthesiologist/Anesthetist must make every effort to maintain masking and thus not reveal a participant's anesthesia level (either assigned or received) to any participants involved in the study, or in any way that permits others to learn the participant's anesthesia level (either assigned or received). To maintain masking, the Study Anesthesiologist/Anesthetist will complete the anesthesia forms (Form 15 Intraoperative Data and Form 16 Anesthesia Data/PACU summary) and will maintain the forms at the clinical center for data entry. No other members of the study team will be able to view the anesthetic record. During the intraoperative study period, the BIS monitor readout will be covered so that the Study Anesthesiologist/Anesthetist remains masked to the BIS numbers while administering propofol so that assessment of depth of sedation during surgery is not influenced by knowledge of the BIS number. Details about masking during treatment are in the MOP. Unmasking is a protocol violation and will be recorded as such on the Protocol Deviation Form (Form 50).

18. Data collection, management, and analysis

Sequence of Form Completion in STRIDE

(all forms available at: \\Jhbcru-fs1\protocoldata\Active\STRIDE\Admin\Forms\LiveFormsByVisit)

Form number and name	When form completed	Information taken from	Who completes form
Form 1 Registration log Form 2 Eligibility Screening (Section A only)	When patient is posted for the Operating Room (OR)	Electronic medical record	Assessment Team/Anesthesiologist
Form 2B Medication (anticoagulant screen)	Morning of surgery, before consent	Electronic medical record and patient interview	Assessment Team
Form 3 MMSE	Morning of surgery,	Patient	Assessment Team

	before consent		
Form 4 Digit Span	Morning of surgery, before consent	Patient	Assessment Team
Form 22 MMSE and DST Over Time	Morning of surgery, before consent	Completed assessments	Assessment Team
Form 5 CAM	Morning of surgery, before consent	Patient	Assessment Team
Form 02 Eligibility Screening (Sections B-G)	Morning of surgery, before consent	Forms 06, 07, 20, 24	Anesthesiologist
Form 40A Evaluation to sign consent	Morning of surgery, before consent	Patient and/or legally authorized representative (LAR)	Assessment Team
Informed consent (Form 40)	Morning of surgery, completion accomplishes consent	Patient and/or LAR	Assessment Team
CONSENT			
Form 12 DRS-R-98	Morning of surgery	Patient	Assessment Team
Form 13 CDR	Morning of surgery	Patient	Assessment Team
Form 8 ADL	Morning of surgery	Patient	Assessment Team
Form 9 IADL	Morning of surgery	Patient	Assessment Team
Form 6 Geriatric Depression Scale	Morning of surgery	Patient	Assessment Team
Form 10 Medication History	Morning of surgery	Electronic medical record	Assessment Team
Form 11 Baseline	Morning of surgery	Patient	Assessment Team
Form 41 Patient Contact Form	Morning of surgery	Patient/Informant	Assessment Team
Form 7 Charlson Comorbidity Index	Morning of surgery, before randomization	Electronic medical record	Assessment Team/Anesthesiologist
Form 70 Emergency Envelope Use: Incident Report	Morning of surgery, at time of randomization, but only if web-based randomization is not used.	Person filling out form provides information	Anesthesiologist
RANDOMIZATION			
Form 15 Intraoperative Data	During surgery	Monitors in operating room	Anesthesiologist
Form 17 Surgery Data Form	After surgery, within one week	X-rays, electronic medical record (surgery notes)	Surgeon
Form 16 Anesthesia/PACU Summary	At discharge from post-anesthesia care unit (PACU)	Anesthesia record and electronic medical record	Anesthesiologist
Form 10 Medication Form 3 MMSE Form 12 DRS-R-98 Form 5 CAM Form 4 DST Form 22 MMSE and DST Over Time Form 29A Delirium	Day 1 Post-operation and each hospital day after until Day 5-post operation or discharge (whichever comes first)	Electronic medical record Patient Nurse/Family/Informant	Assessment Team

Consensus Form			Consensus Panel
Form 10 Medication Form 3 MMSE Form 12 DRS-R-98 Form 5 CAM Form 6 Geriatric Depression Scale Form 8 ADL Form 9 IADL Form 4 DST Form 7 Charlson Comorbidity Index Form 21 Functional Outcomes Form Form 22 MMSE and DST Over Time From 29B Delirium Consensus Form	At one-month clinic or home visit	Patient	Assessment Team Consensus Panel
Form 19 Hospitalization and 30-Days Postoperative Complications	At 30 days after surgery	Electronic medical record Patient	Assessment Team/Anesthesiologist
Form 20 Telephone contact log	Month 2 through Month 11	Patient	Assessment Team
Form 6 Geriatric Depression Scale Form 3 MMSE Form 4 DST Form 8 ADL Form 9 IADL Form 12 DRS-R-98 Form 5 CAM Form 7 Charlson Comorbidity Index Form 13 CDR Form 21 Functional Outcomes Form Form 22 MMSE and DST Over Time Form 32 Study Closeout Form	At one year (home or clinic visit)	Patient	Assessment Team
Form 31 Early Termination Form	When patient dies, leaves study or is lost to follow-up before one-year		Assessment Team
Form 30 Adverse Event Form	Any time during or after intervention that there is an AE	Electronic medical record and person completing form	Assessment Team or Anesthesiologist

488

Forms not in sequence of study (administrative forms)	
Form #	**Form name**
Form 50	Protocol Deviation Log
Form 17	Staff Training Log Sheet

489

490

The following forms are completed during screening

- Registration Log
- Eligibility Screening Form - Part A (Form 02A);
- Eligibility Screening Form - Part B (Form 02B);
- MMSE Form, Form (Form 03);
- Abbreviated DST and Pain Score (Form 04); and
- CAM Form (Form 05).

If the participant meets eligibility criteria for the Study, consent to participate is sought. If the patient is not capable of consenting, we will obtain consent from a legal guardian. We will also administer an "Evaluation of Ability To Give Informed Consent" (Form 40A) to the patient or to the legal guardian before obtaining written consent. A member of the Assessment Team will obtain consent from the patient / guardian and enroll the patient in the research study. If the patient is unable to give informed consent, then the Assessment Team member will seek informed consent from the appropriate family member or guardian. Note that all persons seeking to acquire informed consent will have taken and passed a credentialing test (Form 60) demonstrating knowledge of the STRIDE study and protocol.

If the patient consents to participate in the study, the Baseline Visit is conducted. During the Baseline Visit the following forms are completed. In the rare situation that the patient is taken to the OR emergently, the baseline forms (with the exception of the Geriatric Depression Scale) may be completed with the patient's family member/significant other or with the patient following surgery.

- Geriatric Depression Scale, Short Form (Mood Scale) (Form 06);
- Charlson Comorbidity Index Form (Form 07);
- ADL Form (Form 08);
- IADL Form (Form 09);
- Medication History Form (Form 10);
- Baseline Interview Form (Form 11);
- DRS-R98 Form (Form 12);
- CDR Form (Form 13); and
- Participant Locator Form (Form 41)

Participant assessment during hospitalization

The Assessment Team will complete the forms outlined in the table below for all enrolled participants on a daily basis, beginning on the day after surgery and continuing through postoperative Day 5 or hospital discharge, whichever comes first. When the participant is discharged from the hospital, the Hospitalization Details at Discharge Form (Form 18) should be completed.

Participant assessment following hospitalization

The first scheduled follow-up visit after hospital discharge in STRIDE occurs 30 days postoperatively. The time window for the 1-month follow-up visit is 2 weeks. Visits outside the time window are counted as protocol deviations. The forms completed at this visit are listed in the table below.

Follow-up telephone calls are conducted with all randomized participants over a period of 12 months (1 year) post-surgery. Telephone calls begin at 2 months post-surgery and occur at monthly intervals thereafter until month 11. At each telephone follow-up call, participants are asked where they are currently living, whether there have been any changes in their health status since the last telephone call, and whether there have been changes in the contact information for the people listed on the Participant Locator Form (Form 41). This information is recorded on the Participant Telephone Contact Form (Form 20). Contact attempts are recorded on the Contact Log (Form 55). The time window for the monthly follow-up calls is two weeks, and any call not taking place within this window is considered a late telephone visit. Participants may also completely miss a telephone call. Participants who "miss" two consecutive follow-up calls are considered "inactive" until they are reinstated. Efforts to reinstate inactive participants should be pursued vigorously.

The second scheduled follow-up after hospital discharge in STRIDE is 1 year postoperatively (the 12-month follow-up visit). The time window for the 12-month visit is 4 weeks. Visits outside the time window are counted as protocol departures. The forms completed at this visit are listed in the table below.

Although there are no required clinical center visits between the 1-month follow-up visit and the 12-month follow-up visit, it is expected that some randomized participants may have additional visits, "Unscheduled Visits or Hospitalization," for re-hospitalization, adverse events or other reasons. The Recruitment & Interview Team is not required to collect specific data on these visits, unless a participant death occurs or the participant withdraws consent.

If any STRIDE visit or telephone follow-up contact is missed and will not be completed, a Missed Forms or Visit Form (Form 52) must be completed as well as a Protocol Deviation Form (Form 50).

If, at any time, the participant cannot be located, an intensive search should be instituted immediately, even if the participant has not missed a visit. The steps taken to locate the participant should be documented. If a participant cannot be located, the STRIDE Investigators Executive Committee reviews the participant's record and formulates recommendations for action.

As soon as the Recruitment & Interview Team personnel become aware that a participant has died, a Notice of Early Termination or Death Form (Form 31) must be completed. The Study Closeout Form (Form 32) must also be completed. If the death occurs within 30 days of the Study surgery, an Adverse Event Report Form (Form 30) must be completed.

Follow-up Visits for Participants in STRIDE

Visit	Form Required	When
Day 1-5 After Surgery	• MMSE Form (Form 03) • Abbreviated DST and Pain Score Form (Form 04) • CAM Form (Form 05) • MMSE and DST Scores Over Time (Form 22) • Medication History Form (Form 10) • DRS-R-98 Form (Form 12)	Each inpatient day 1-5 following surgery, until hospital discharge.
Hospital Discharge	• Hospitalization Details at Discharge Form (Form 18)	At participant discharge.
1-Month Follow-up Visit	• MMSE Form (Form 03) • Abbreviated DST and Pain Score Form (Form 04) • CAM Form (Form 05) • MMSE and DST Scores Over Time (Form 22) • Geriatric Depression Scale, Short Form (Mood Scale) (Form 06) • Charlson Comorbidity Index Form (Form 07) • ADL Form (Form 08) • IADL Form (Form 09) • Medication History Form (Form 10) • DRS-R-98 Form (Form 12) • 30-day Postoperative Occurrences Form (Form 19) • Functional Outcomes Form (Form 21) • Contact Log (Form 55)	30 days after surgery
Month 2 After Surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Two months after surgery
Month 3 After Surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Three months after surgery
Month 4 After	• Contact Log (Form 55)	Four months after

Surgery	• Participant Telephone Contact Form (Form 20)	surgery
Month 5 After Surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Five months after surgery
Month 6 After Surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Six months after surgery
Month 7 After Surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Seven months after surgery
Month 8 after surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Eight months after surgery
Month 9 After Surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Nine months after surgery
Month 10 After Surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Ten months after surgery
Month 11 After Surgery	• Contact Log (Form 55) • Participant Telephone Contact Form (Form 20)	Eleven months after surgery
12-Month Follow-up Visit	• MMSE Form (Form 03) • Abbreviated DST and Pain Score Form (Form 04) • CAM Form (Form 05) • MMSE and DST Scores Over Time (Form 22) • Geriatric Depression Scale, Short Form (Mood Scale) (Form 06) • Charlson Comorbidity Index Form (Form 07) • ADL Form (Form 08) • IADL Scale Form (Form 09) • DRS-R-98 Form (Form 12) • CDR Form (Form 13) • Functional Outcomes Form (Form 21) • Study Closeout Form (Form 32) • Medication History Form (Form 10)	Twelve months after surgery

Overview of testing points:

Assessment	**Time Point**			
	Pre-op	**POD1 and thereafter**	**1-month**	**1-year**
MMSE	x	x	x	x
DST	x	x	x	x
DRS-R-98	x	x	x	x
CAM	x	x	x	x
Geriatric Depression Scale	x		x	x
CDR	x			x
IADL	x		x	x
ADL	x		x	x
Pain score	x	x	x	x

Drug data	x	x	x	x
Co-morbidities	x		x	x
Hand grip			x	x
Walking speed			x	x
Chair stand speed			x	x

Pre-op: preoperative
PO: postoperative

18a. Data management

Forms related to research study data are entered into a REDCap database developed for the STRIDE project (see www.Project-REDCap.org for more information on REDCap). The STRIDE REDCap database contains edit checks to support data quality and completeness. These edit checks identify data that is out-of-range, missing, or potentially in conflict with other data. Data quality and completeness reports will be developed to monitor the quality of the data. Additionally, REDCap supports "skip" logic to ensure that data are entered appropriately.

The tracking system built using STRIDE Project Tracker enables the Recruitment & Interview Team to monitor the flow of participants and data through the protocol; and to assist in maintaining appropriate contacts with patients. The system also tracks that the necessary contacts are being made ensuring that study participants are closely followed.

REDCap accommodates 'form specific' access control. This provides a mechanism for allowing different study team members to access different forms. Specifically, certain member will have access to ONLY treatment data, while a different group will have access to all other study data. This ensures that only appropriate study team members have access to treatment assignment data and outcomes data.

REDCap includes robust account and access control functionality. User accounts and groups are maintained by the Database Manager. Each user is granted only the appropriate levels of access to REDCap features, functionality, and data. For example, the Study Statistician might have access to download an analysis database, but would not be granted access to the data entry environment. Additionally, access can be granted at the "form" level. This helps to ensure proper masking of data, as deemed necessary and appropriate.

18b. Data entry

A two-phase data entry model will be implemented for the STRIDE REDCap database. All data will be entered into the STRIDE REDCap database by one of the Assessment Team members. Initially, each entered form will be left in an 'unverified' state. Subsequent to initial entry, the STRIDE 'reviewer' will compare what was entered with what is on the original forms. Any necessary corrections are made, the entered form is marked as 'Complete' in the software and the record is 'locked', preventing future changes. These steps help to ensure a high standard of data quality. By utilizing the built-in features of 'record state' (unverified and complete) and the ability to 'lock' records, the progression of data entry can be monitored to ensure timely and accurate data entry. REDCap also includes an extensive audit trail. Changes to records and fields are captured, including the prior value, when the change was made, and by whom.

REDCap training is provided for those using REDCap and/or the STRIDE Project Tracker database. As staff or roles change, addition training will be provided. Support for system usage is made available as necessary. Additional training materials will be generated as deemed appropriate and necessary.

19. Quality assurance

Trial Oversight and Coordination has overall responsibility for developing and implementing quality assurance and monitoring for STRIDE. Performance monitoring reports are prepared by Trial Oversight and Coordination using the definitions outlined below. Trial Oversight and Coordination uses these reports to identify whether special training or assistance is required and to prepare training sessions.

19a. Definitions of STRIDE protocol violations, deviations, and departures

Violations: a breach of STRIDE protocol resulting in an adverse effect on the scientific integrity of the study. Protocol violations include, but are not limited to:

- Failure to perform the assigned anesthesia (i.e., crossovers to opposite treatment, no surgery);
- Permitting a person or persons that have not met the requirements for the study to participate in STRIDE procedures (e.g., uncertified personnel administering the assigned anesthesia);
- Committing willful or repeated infractions that may affect study outcomes (e.g., unmasking of study personnel); and
- Engaging in fraudulent acts that could be construed as either illegal or unethical or undermining the validity or reliability of study data (e.g., deliberately enrolling an ineligible participant or purposely providing inaccurate information on forms).

Deviations: an error or infraction of STRIDE protocol that may compromise the ability to measure reliably any study outcome. Protocol deviations include, but are not limited to:

- Performing inadvertently or unintentionally a prohibited STRIDE procedure on no more than one occasion (e.g., mistakenly enrolling an ineligible participant);
- Conducting inadequate follow-up of an enrolled participant (e.g., losing track of a randomized participant); and
- Inadequately performing or documenting a study procedure (e.g., inadequate eligibility screening).

Departures: the occurrence of a study visit outside of the established time frames. Protocol departures may adversely affect the study outcome especially if they happen on multiple occasions, and are monitored as an element of clinical center performance.

19b. Definitions of screening failure or subject removal criteria

Patients defined as “screening failures” are those patients who are not eligible on one of the screening measures (e.g., MMSE failure, excluded medication on Form 2B). These patients are not eligible to be consented.

Patients defined as “Consented/Non-randomized” are those who become ineligible for the study after they have already consented, e.g., patients for whom we are unable to achieve a satisfactory level of spinal anesthesia, or consented patients discovered to have taken clopidogrel or other disqualifying drug within 7 days of surgery.

The “subject removal criterion” is refusal of the consented patient to participate in follow-up.

20. Statistical methods

20a. Covariates

Randomization theory implies that there will be no confounding variables, and thus that no other independent variables need to be included in the regression models for adjustment to obtain an unbiased estimate of treatment effect. Nevertheless, the treatment groups will be compared on baseline medical, social, and demographic variables, to find any variables with important distributions that are different between groups, and any such discrepant variables will be examined for possible confounding in the regression analyses. In addition, these variables will be investigated to determine whether their inclusion in the regression model improves the precision of the estimate of the treatment effect.

Although the stratification variables of participant age and dementia status will most likely be balanced

between the two intervention arms, we will include them as covariates in the analysis to reduce outcome variability associated with these two factors. For exploratory analyses of the primary and secondary outcomes in relation to the measures of actual level of sedation, the data will be treated as observational, and potential confounders will be identified based on a priori knowledge and /or their associations with the outcome and predictor of interest in such analyses.

20b. Preliminary analysis

Standard preliminary analyses will include examining distributions and computing rates or means and standard deviations for all variables at each observation point, and comparing rates or means in the two treatment groups. For the main study analyses comparing the two treatment groups, logistic regression, Poisson regression, and survival analysis methods will be used, as described below.

20c. Primary analysis

The primary analysis for the STRIDE trial will test the contrast comparing the probabilities of a patient having any in-hospital (days 1-5) delirium between the randomly assigned intervention groups (deep versus light sedation) according to the intention-to-treat approach. The predictor of interest is the intervention group assignment, and participants will be included in the group to which they were randomly assigned regardless of sedation level actually received.

First, we will conduct logistic regression, with the primary outcome variable (any in-hospital delirium, yes/no) as the binary outcome and the intervention group assignment the primary predictor variable in the model. The model will include relevant baseline characteristics found to be unbalanced between intervention groups, and the stratification variable of age and pre-hospital dementia status as covariates. The adjusted odds ratio estimate derived from the model could be easily converted to adjusted relative risk estimate given that the marginal probability for the binary outcome will be estimable under the trial design.

We do not expect missing data for the primary outcome as supported by our preliminary trial data. In the rare event that death or other sever medical events during operation or immediately post-surgery (i.e., days 1-5) would prevent full assessment of the outcome value for that randomized participant, the following approach will be adopted for data analyses.

Let Y denote the primary outcome of in hospital post-operative delirium, X the predictors (intervention group assignment variable and included baseline covariates), and D the binary variable of death prior to discharge (coded as 1 = yes, 0 = no). The goal of the primary analysis is to model Pr(Y | X), which can be decomposed using conditional probabilities:

$$\Pr(Y \mid X) = \Pr(Y \mid D = 0, X) \bullet \Pr(D = 0 \mid X) + \Pr(Y \mid D = 1, X) \bullet \Pr(D = 1 \mid X),$$

where Pr(Y | D = 1, X) is not observable. Note that Pr(D | X) is estimable, and in the event that Pr(D = 1 | X) is very small, which is expected as we observed no death prior to discharge in our preliminary trial, $\Pr(Y \mid X) \approx \Pr(Y \mid D = 0, X)$. Therefore, when no or very few deaths occur before discharge, we do not expect to incur much bias in our inferences by approximating the primary analysis goal of Pr(Y | X) with modeling of Pr(Y | D = 0, X), which is estimable based on the observed data.

In the case where $\Pr(Y, D \mid X) = \Pr(Y \mid X) \bullet \Pr(D \mid X)$, or equivalently $\Pr(Y \mid X) = \Pr(Y \mid D, X)$, the random process for death prior to discharge (D) is conditionally independent of the outcome values (Y), given the intervention group assignment and relevant baseline covariates (X). In such case, the missing data in Y due to death (D = 1) is considered “missing at random” (MAR), and the inferences on Pr(Y | X) based on modeling Pr(Y | D = 0, X) using data with observed Y values only, though inefficient, will still be valid. Whether data missing is MAR or not cannot be empirically verified without auxiliary data on the missing Y values, so we must also contemplate the possibility of non-MAR missing data process. To evaluate the potential impact of non-MAR missing data processes on our inferences based on the observed data, we will conduct sensitivity analyses though multiple imputation of missing data from models of Pr(Y | D = 1, X) deviated from the assumed model of Pr(Y | D = 1, X) under various scenarios.

In addition, we will utilize repeated assessments of delirium during the hospital stay while accounting for the potentials for different length of hospital stay (LOS). The average LOS for elderly hip fracture participants is 3 days. We will code a participant as having a recurrent delirium in hospital if this participant had a previous delirium positive assessment, followed by at least one negative daily delirium assessment prior to the new assessment of positive delirium while still in hospital. We will use Poisson regression model with over dispersion (i.e. negative binomial model), offset by person-day of observation based on LOS, to estimate in hospital incidence of delirium for each intervention group while accounting for the potential variance inflation due to recurrent events from the same participant. Rate ratio and corresponding 95% confidence interval (CI) comparing incidence between the two intervention groups will be calculated using robust estimates. The analysis will be based on intention-to-treat, and covariates will be included for model adjustment as appropriate. Further analyses will stratify the analysis by evidence of baseline co-morbidities, to account for the longer length of hospital stay (LOS) for sicker participants.

20d. Secondary Analysis

Secondary analysis will compare the main secondary outcome of mortality at 1 year (12 months) following surgery between intervention groups by the intention-to-treat approach.

Mortality at 1-year:

For the outcome of time from surgery to death by the end of the 1-year (12-month) follow-up, outcome assessment will be done through regular phone contact with family members and search of the National Death Index, Social Security Death index, and obituaries, and exact date of death will be ascertained. Time to death from the surgery date will be calculated based on date of death. Based on data and experiences garnered from the preliminary trial, we expect very little missing data in this outcome. The secondary analysis will test the contrast for this outcome by comparing the risk of mortality over 1-year after surgery between the randomly assigned intervention groups.

To explore the difference in cumulative mortality between the intervention groups, we will conduct Kaplan-Meier analysis to estimate the nonparametric 1-year survival curves for both intervention groups. The difference between the two survival curves will be tested using the log-rank test. Relative risk of 1-year mortality comparing the heavy sedation to the light sedation intervention group will be evaluated through estimated hazard ratios from the semi-parametric Cox proportional hazards model, with corresponding confidence intervals. The main model will have intervention group assignment as the primary predictor and include the same covariates as in the model for the primary analysis. Additional models will be constructed to explore the potential impact of covariates over time on the mortality outcome during the 1-year follow-up. For example, a model include the primary outcome variable of delirium status in hospital as an additional covariate could provide insight on whether the impact of depth of sedation on 1-year mortality might be mediated, at least partially, through postoperative delirium. Other variables collected preoperatively (such as the Charlson Co-Morbidity Index), perioperatively, or during follow-up can be used in additional multivariable modeling as appropriate. Information collected at baseline and updated during the follow-up will be used as time-dependent covariates to better reflect a dynamic covariate process over time. The proportional hazards assumption will be evaluated by examining the intervention group by survival time interaction term in the proportional hazards model as well as by examining the Schoenfeld residuals.

20e. Other analyses

Other analyses will include analyses of the maximal delirium severity scores in hospital and prevalence of delirium at 1-month post surgery, subgroup analyses of the primary and secondary outcomes (for example, subgroups based on baseline comorbid conditions), exploratory analyses of the primary and secondary outcomes in relation to the measures of actual level of sedation such as OAAS levels and BIS measures recorded, and other analyses related to tertiary outcomes.

Maximal delirium severity score:

The maximal delirium severity score is defined as the highest DRS-R-98 score recorded during postoperative (in-hospital) Day 1 to Day 5 or to hospital discharge (whichever occurs first). A relevant implicit assumption for using this outcome definition is that study participants reach their maximal DRS-R-

98 scores while in hospital. This will be the case if study participants who are discharged prior to postoperative Day 5 are delirium free between discharge and postoperative Day 5, so that the largest delirium severity based DRS-R-98 scores during the defined period will be observed in hospital prior to discharge. Examination of patients in our preliminary trial who were discharged before Day 5, and were discharged to the Bayview rehabilitation center (one of several used by discharged patients in that study) supports the validity of this assumption. We expect none or very little missing data (due to death prior to discharge, see details in discussions related to the primary outcome and primary analysis) in this outcome. Analysis for this outcome will test the contrast comparing the mean maximal delirium severity scores between the randomly assigned intervention groups.

Generalized linear models will be used to derive and compare the adjusted mean maximal severity scores between the randomly assigned intervention groups. The model will have intervention group assignment as the primary predictor and include the same covariates as in the model for the primary analysis. Ninety-five percent confidence intervals for the adjusted mean group differences will be computed. Transformation of outcome will be performed as necessary. Residual analysis will be conducted to ensure validity of model assumptions. The general approach for handling missing outcome data will be similar to that described for the primary analysis.

Delirium at 1-month:

There will be no formal delirium assessment prior to the 1-month (30-day) post-surgery office visit after discharge. We anticipate that a small number of participants will die before the one-month follow-up, while 75% of those who are alive at one-month will come back to the hospital for a follow-up visit and the rest of those alive would require a home visit. The analysis will follow two-part modeling, with the first part modeling the probability of death at the 1-month follow-up, and the second part modeling the probability of having delirium among those who are still alive at 1-month post surgery.

Here let Y denote the delirium outcome at 1-month, X the predictors (intervention group assignment variable and included covariates), and D the binary variable of death prior to 1-month (coded as 1 = yes, 0 = no). The goal of this analysis is to model Pr(Y | X), which can be decomposed using conditional probabilities:

$$\Pr(Y \mid X) = \Pr(Y \mid D = 0, X) \cdot \Pr(D = 0 \mid X) + \Pr(Y \mid D = 1, X) \cdot \Pr(D = 1 \mid X),$$

where Pr(Y | D = 1, X) is not observable. Note that Pr(D | X) is estimable, and in the event that Pr(D = 1 | X) is very small, $\Pr(Y \mid X) \approx \Pr(Y \mid D = 0, X)$. Therefore, we do not expect to incur much bias in inferences by approximating Pr(Y | X) with modeling of Pr(Y | D = 0, X), which is estimable based on the observed data, if very few deaths occur before discharge,

In the case where $\Pr(Y, D \mid X) = \Pr(Y \mid X) \cdot \Pr(D \mid X)$, or equivalently $\Pr(Y \mid X) = \Pr(Y \mid D, X)$, the random process for death prior to discharge (D) is conditionally independent of the outcome values (Y), given the intervention group assignment and relevant baseline covariates (X). In such case, the missing data in Y due to death (D = 1) is considered “missing at random” (MAR), and the inferences on Pr(Y | X) based on modeling Pr(Y | D = 0, X) using data with observed Y values only, though inefficient, will be valid. Whether data missing is MAR or not cannot be empirically verified without auxiliary data on the missing Y values, so we must consider the possibility of non-MAR missing data process. We will conduct sensitivity analyses though multiple imputation of missing data from models of Pr(Y | D = 1, X) deviated from the observed model of Pr(Y | D = 1, X) under various scenarios to evaluate the potential impact of non-MAR missing data processes on our inferences based on the observed data.

The model will be logistic regression-based and will include the intervention group assignment as the primary predictor as well as the same covariates as in the model for the primary analysis. Additional models will be constructed to explore the potential impact of covariates over time on the risk of delirium at 1-month follow-up. For example, a model that includes the primary outcome variable of delirium status in-hospital as an additional covariate could provide insight on whether the impact of depth of sedation on longer term delirium risk might be mediated, at least partially, through postoperative delirium in-hospital. Variables collected preoperatively, perioperatively, or during the 1-month follow-up assessments (e.g.,

depression status, medication use, and the Charlson Co-Morbidity Index) can be used in multivariable modeling as appropriate. Odds ratio estimates can be easily converted to relative risk estimates since we will be able to estimate marginal risk of delirium at the 1-month follow-up. Ninety-five percent confidence interval for the corresponding estimates will be computed.

20f. Subgroup analyses

We will explore potential differentiation of intervention effects by age, gender, or other demographic and clinical characteristics. The subgroup analyses will be performed both alone (only the data from the subgroup used in the regression) and also with all of the subgroup data combined with the use of cross product term of subgroup indicator variable by treatment indicator variable to evaluate subgroup by treatment interaction; estimates of the treatment effect for each level of the subgroup variable will be reported. These analyses will be exploratory for the purposes of generating hypotheses for future studies.

20g. "On-treatment" analysis

OAA/S levels or BIS values monitored over time in the operating room will be characterized into different "exposure" patterns and related to the outcomes of the study. For example, these analyses could explore whether observed associations are more likely to be related to the amount of cumulative exposure (area under the curve of OAA/S levels or BIS values over time during operation), peak exposure (maximal OAA/S levels or BIS values during operation), or cumulative "exposure" level above certain thresholds. These exposure variables could have overlapped values between the randomly assigned treatment groups, and will be treated as observational data so that potential confounding will have to carefully evaluated and managed as in any observational studies.

20h. Analysis of adverse events

Analyses of adverse events and related intervention safety issues will be reported to the DSMB at their periodic meetings, as well as trial performance with respect to participant recruitment and follow-up, and completeness and timely entry of study data, and corrections made to the database.

20i. Interim analysis

No interim data analyses will be conducted as discussed with the DSMB.

20j. Missing Data

Prevention of missing data is far superior to post hoc statistical treatment for missing data. Every effort will be made to ensure proper and complete data collection. We expect to have few missing data points on postoperative delirium evaluation in-hospital, although lack of data caused by death or other medical reason is possible. We expect little attrition at 1-month follow-up given that our follow-up protocol will include an option for a home visit. We also expect to have few missing data on the mortality outcome at 1-year as our preliminary trial has flushed out a reliable process to ascertain deaths in the target patient population within our catchment area.

Our main approach for handling missing data, when it occurs, will be conducting analyses under the assumption of data missing at random (MAR), where valid inferences can be achieved through multiple imputations or a maximum likelihood approach using correct models for the observed data. However, the validity of the MAR assumption cannot be empirically verified without auxiliary data / information on the missing values. Therefore, we will supplement our MAR analyses with carefully planned sensitivity analyses to check for the robustness of our inferences under various plausible non-MAR scenarios. For example, for those with persistent delirium in previous evaluations, it is more likely that the missing observation will also be positive on delirium. Hence it may be more reasonable to impute such missing values based on an appropriately constructed imputation distribution with high probability of being positive on the delirium outcome. We will include sensitivity analyses though multiple imputation of missing data from models deviating from the observed model under various scenarios deemed plausible by the DSMB as well as experts with extensive experience in delirium research.

21. Protocol risks and participant protection

The potential risks to subjects for the proposed study include difficulties adhering to study protocol, psychological risks associated with cognitive testing and risks to privacy and confidentiality. Each is discussed separately.

21a. Medical risks and expected frequency

This study examines different sedation levels; we are not interested in studying patients who require intubation to maintain their airway as this adds an additional variable to the study. From a safety perspective, as seen in our preliminary data, neither level of sedation incurs increased risks in terms of hypotension or airway compromise during spinal anesthesia with propofol sedation.

Psychological risks associated with neuropsychological testing are generally irritation at the question set, with many patients suggesting that the questions are unwise. In addition, subjects who are evidently having a hard time completing the battery frequently get frustrated. There is no permanent injury associated with either the dementia or delirium testing batteries, and staff will be trained to minimize any irritation and to be supportive of the study participants.

Whenever protected health information is collected, there are potential risks to privacy and confidentiality. All personnel will be trained to assure compliance with the HIPAA regulations. The data collection instruments will be stored in secure locations, and the database will only contain coded information. The key to the code will be maintained within locked file cabinets.

There are no currently approved treatments for delirium. For the proposed study, the only true alternative is not to participate.

21b. Confidentiality

We will be collecting demographic information, in addition to the study information. All information collected will be handled per institutional protocol for protected health information.

22. Consent

Written informed consent is obtained from all STRIDE participants. There is no payment for study subjects. The Assessment Team members are the persons conducting the informed consent discussion with the subject. Consent will be obtained pre-operatively, in the patient's hospital room or in the emergency room if the patient has not been transferred to a hospital room. The time allotted for obtaining consent is 30-40 minutes. The reading level of the consent form is Grade 7.9 Flesch-Kincaid level, per Microsoft WORD 2007. Comprehension of the consent information will be assessed by asking patients to state in their own words the concepts research staff had presented to them. An "Evaluation to Give Consent" form is filled out and witnessed for each patient before consent can be obtained. The same guidelines used for surgical and anesthetic consent are applied to this protocol's consent if some or all subjects are cognitively impaired or have language/hearing impairment. All consent forms and informative materials are written, and all testing is oral. Inclusion criteria require the ability to read/write/hear/speak/understand English. Inability of the person giving informed consent to speak/read/write/understand/hear English is an exclusion criterion.

23. Data and safety monitoring plan

23a. DSMB composition

The DSMB consists of five members and three members usually constitute a quorum. Members are recommended by the PI and /or NIA Program Official, and the NIA Director approves the composition of the DSMB and its membership. Membership consists of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Collaborators or associates of Dr. Sieber are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required.

The DSMB includes experts in or representatives of the fields of:

- internal medicine,
- epidemiology

- biostatistics
- psychiatry
- anesthesiology.

Dr. Jeff Carson, of UMDNJ-Robert Wood Johnson Medical School, has been selected by NIA in consultation with the PI to serve as the Chairperson and is responsible for overseeing the meetings, developing the agenda in consultation with the NIA Program Official and the PI. The Chair is the contact person for the DSMB. The *Johns Hopkins Medical Institutions* shall provide the logistical management and support of the DSMB. A medical safety officer (MSO) will be identified at the first meeting and is typically a physician independent of the DSMB. The MSO will be the contact person for serious adverse event (SAE) reporting. Procedures for notifying the Chair of the DSMB and the NIA Program Official will be discussed at the first meeting.

23b. DSMB responsibilities

The DSMB will have the authority to stop the study either because the hypotheses have been confirmed or denied, or because adverse events (AE) or SAEs are detected that require the study to be terminated or redesigned. In the case of concerns of futility not clearly associated with safety issues, the DSMB will be advisory to NIA and the PI. The PI is responsible for notifying the IRB of significant unanticipated events. The DSMB is responsible for reviewing all these events and overseeing PI activities related to safety information. The DSMB reports as well as any actions taken will be reported to the IRB.

Early in the trial, DSMB review will focus more on safety, quality of conduct, and trial integrity rather than on efficacy evaluation. Later meetings may include formal efficacy or futility analyses. Early DSMB reports will focus on simple descriptions of the demographic and diagnostic characteristics of the study population and on the baseline data collected. Subsequent reports will include tabulations of this sort, as well as a variety of more sophisticated analyses to draw inferences regarding study results. The DSMB will discharge itself from its duties when the study is complete.

Specifically, the DSMB responsibilities are to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- advise the NIA on the readiness of the study staff to initiate recruitment;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the clinical center, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the PI;
- protect the safety of the study participants;
- report to NIA on the safety and progress of the trial;
- make recommendations to the NIA, the PI, and, if required, to the Food and Drug Administration (FDA) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- if appropriate, review interim analyses in accordance with stopping rules, which are clearly defined in advance of data analysis and have the approval of the DSMB;
- ensure the confidentiality of the study data and the results of monitoring; and,
- assist the NIA by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

23c. DSMB process

At the first meeting the DSMB will discuss the protocol, suggested modifications, and establish guidelines to study monitoring by the Board. The DSMB Chairperson in consultation with the PI and the NIA

Program Official as needed, will prepare the agenda to address the review of study materials, modifications to the study protocol and informed consent document, initiation of the trial, appointment of a safety officer, as needed, reporting of adverse events, statistical analysis plan including interim analysis and stopping rules, etc.

Meetings of the DSMB will be held at least once a year at the call of the Chairperson. The NIA Program Official or designee will be present at every meeting. An emergency meeting of the DSMB may be called at any time by the Chair or by the NIA should participant safety questions or other unanticipated problems arise.

Meetings shall be closed to the public because discussions may address confidential participant data. Meetings are attended by the PI and members of his/her staff. Meetings may be convened as conference calls as well as in-person. All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

23d. DSMB meeting format

DSMB meetings will consist of open and closed sessions. Discussion held in all sessions is confidential. The PI and key members of the study team attend the open sessions. Open session discussion will focus on the conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered. Unblinded data are not presented in the open session. The closed session will be attended by the DSMB members and the NIA representative(s). The study statistician may be present, at the request of the DSMB. Any data by blinded study group and, as necessary, unblinded data, are presented during the closed session.

If necessary, an executive session will be attended by voting DSMB members and the NIA staff and their representatives. The executive session will be held to identify and discuss the DSMB's recommendations to the NIA. The study staff may be present, at the request of the DSMB, during the executive session.

Each meeting must include a recommendation to continue or to terminate the study made by a formal DSMB majority or unanimous vote. A formal report containing the recommendations for continuation or modifications of the study will be prepared by the DSMB Chairperson. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required. In the event of a split vote, majority vote will rule and a minority report should be appended. The DSMB Chair provides the tiebreaking vote in the event of a 50-50 split vote.

A recommendation to terminate the study may be made by the DSMB at any time by majority vote. The Chair should provide such a recommendation to the NIA immediately by telephone and email. After the NIA Director makes a decision about whether to accept or decline the DSMB recommendation to terminate the study, the PI is immediately informed about his decision.

23e. Publication of results

The DSMB should be given the opportunity to read and comment on any publications before submission. DSMB members should be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DSMB meetings should be included in the body of the main report. The DSMB may discuss issues from their involvement in the trial no sooner than 12 months after the primary trial results have been published, or when permission is agreed with the overseeing committee.

23f. Role of MSO

The STRIDE Trial MSO will serve in an advisory capacity to the STRIDE Trial DSMB and the STRIDE investigators executive committee to monitor patient safety.

<u>SAEs</u>

The MSO will review all SAEs submitted to the IRB from the clinical site.
The process for the SAE review is as follows:

1. Trial Oversight and Coordination will notify the PI of any SAE and they will jointly prepare a draft SAE report for IRB submission. It is the responsibility of the PI to finalize the SAE report and narrative summary and submit to the IRB. Trial Oversight and Coordination will forward the SAE report to the MSO via e-mail following receipt of the SAE narrative.
2. The MSO will review the SAE narrative and notify Trial Oversight and Coordination whether additional information is needed in making any study related decisions.
3. If additional information is needed, Trial Oversight and Coordination will contact the clinical study team and any requested additional information will be obtained and transmitted to the MSO.
4. The MSO will review all SAE materials and reply to the original SAE notification e-mail with a determination regarding whether or not the reported event was:
   a) related to the study protocol using one of the following categories:
      definitely related;
      probably related;
      indeterminate;
      unlikely to be related;
      definitely unrelated.
   b) whether the SAE was expected or unexpected.
5. Trial Oversight and Coordination will send SAE reports to the NIH Project Officer and the DSMB chairperson at the same time. These individuals will review the report, may consult with the MSO and may decide to convene the DSMB to discuss issues related to monitoring such events. The DSMB, as an advisory body to the NIA, may advise early termination of the trial for safety reasons or make other recommendations regarding modifications to the protocol.
6. A report of all AEs (both serious and non-serious) will be compiled every 12 months during subject recruitment and shared with the MSO, DSMB chair, and NIA Project Officer.

Definitions:

SAE

An adverse event will be considered to be serious if it is or results in any of the following:

- death;
- life-threatening;
- inpatient hospitalization or prolongation of existing hospitalization;
- significant or permanent disability;
- medical intervention to prevent permanent damage (e.g., intensive emergency treatment of allergic bronchospasm; blood dyscrasias or convulsions not requiring inpatient hospitalization; development of drug dependency or drug abuse).

Related to STRIDE protocol

The phrase “related to the STRIDE protocol” implies related or possibly related to participation in the research, i.e., is there a definite or reasonable possibility that the incident, experience or outcome may have been caused by the study intervention.

Unexpected

The term unexpected refers to an adverse event that has not been previously known or expected to be associated with the study procedures and clinical population involved in the STRIDE protocol. It is judged in terms of the nature, severity or frequency of the event, given the research protocol, IRB approved informed consent document, and other sources of information, and relative to the characteristics of the subject population being studied (expected natural progression of subject’s disease, disorder or condition or predisposing risk factors).

References:

1. Rasmussen LS, JT M. Central nervous system dysfunction after anesthesia in the geriatric patient. *Anesthesiol Clin North America*. 2000;18(1):59-70.

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3. Pandharipande P, Jackson J, Ely EW. Delirium: Acute cognitive dysfunction in the critically ill. *Curr Opin Crit Care*. 2005;11(4):360-368.
4. Pandharipande P, Ely EW. Sedative and analgesic medications: Risk factors for delirium and sleep disturbances in the critically ill. *Crit Care Clin*. 2006;22(2):313-27, vii.
5. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc*. 2010;85(1):18-26.

Table 1: Observer's assessment of alertness/sedation scale (OAA/S)

Response	Score Level
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimuli	0