Supplement to Vail EA, Feng R, Sieber F, et al.

Long-term outcomes with spinal versus general anaesthesia for hip fracture surgery

Protocol versions and summary of changes

1. Initial approved study protocol (version date: August 22, 2015)
2. Final study protocol (version date: March 29, 2016)
3. Summary of changes

Manuscript ID: *TBD*
Protocol Title: *Long-term outcomes with spinal versus general anaesthesia for hip fracture surgery*

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Perelman School of Medicine
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A RANDOMIZED CONTROLLED TRIAL OF REGIONAL VERSUS GENERAL ANESTHESIA FOR PROMOTING INDEPENDENCE AFTER HIP FRACTURE (REGAIN TRIAL)

A multicenter randomized controlled trial to compare survival, functional recovery, and cognitive outcomes, and postoperative adverse events among patients aged 50 and older receiving spinal versus general anesthesia for hip fracture surgery.

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Funding sponsor	Patient Centered Outcomes Research Institute 828 L St., NW, Suite 900 Washington, DC 20036 Phone: (202) 827-7700 Fax: (202) 355-9558
Grant Number	PCS 1406-18876
Interventions	Standard care spinal anesthesia Standard care general anesthesia
ClinicalTrials.gov Number	NCT02507505

Initial version: A2.2 **-** August 22, 2015

OCR
Office of Clinical Research

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List of Abbreviations

3D-CAM: 3-minute Diagnostic Assessment for CAM-Defined Delirium

AE: Adverse Event

BPI: Brief Pain Inventory

CCC: Clinical Coordinating Center

CRC: Clinical Research Coordinator

DCC: Data Coordinating Center

DSMB: Data Safety Monitoring Board

IRB: Institutional Review Board

NSQIP: National Surgical Quality Improvement Program

OAAS: Observer's Assessment of Alertness/Sedation Scale

PI: Principal Investigator

REGAIN: Regional versus General Anesthesia for promoting Independence after Hip Fracture

SBT: Short Blessed Test of cognition

WHODAS 2.0: WHO Disability Assessment Schedule 2.0

Investigator Approval Statement

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with the University of Pennsylvania Clinical Coordinating Center and Data Coordinating Center during the study. I will adhere to the Declaration of Helsinki and its amendments, the International Conference on Harmonization (ICH) principles of Good Clinical Practice (GCP; including archiving of essential study documents) and all applicable regulations and guidelines of the country in which the study is conducted.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

REGAIN

A Randomized Controlled Trial of Regional versus General Anesthesia for Promoting Independence after Hip Fracture

Final Protocol: August 22, 2015

Study Summary

Title	**A Randomized Controlled Trial of Regional versus General Anesthesia to Promote Independence after Hip Fracture (REGAIN Trial)**
Short Title	REGAIN Trial
Methodology	Randomized, active-controlled trial
Study Duration	6 years
Single or multicenter design	Multicenter
Objectives	**1.** To test the effect of spinal versus general anesthesia on recovery of walking at 60 days after randomization. **2.** To measure the impact of spinal versus general anesthesia on overall health and disability, return to the pre-fracture place of residence, pain, and mortality, and cognition at approximately 60, 180 and 365 days after randomization **3.** To assess the tolerability of spinal versus general anesthesia for hip fracture surgery, and the association of spinal versus general anesthesia with inpatient mortality and major morbidity, including postoperative delirium.
Number of Subjects	Total enrollment (consented patients): 2,424; Total randomized sample: 1,600
Main Inclusion and Exclusion Criteria	**Inclusion criteria:** Hip fracture requiring surgical treatment; age ≥ 50 years; ability to walk without human assistance before fracture **Exclusion criteria:** Concurrent surgery not amenable to spinal anesthesia; absolute contraindications to spinal anesthesia; patients known or suspected to be at elevated risk for malignant hyperthermia; periprosthetic fracture; and by determination of the surgeon, the treating anesthesiologist, or the site Clinical Director or their designate.
Interventions	Standard care spinal anesthesia Standard care general anesthesia
Statistical Methodology	Data will be analyzed via intent-to-treat (primary) and per-protocol methods; binary outcomes will be analyzed using standard two-sample hypothesis tests and multivariate regression models accounting for necessary stratification factors.
Safety Evaluations	Safety evaluations will occur via medical record review on postoperative day 1-3 and at discharge for selected serious adverse events.
Data and Safety Monitoring Plan	The PI and the DSMB will be responsible for monitoring the data quality and the ongoing safety of subjects.

BACKGROUND AND STUDY RATIONALE

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (GCP) (International Conference on Harmonization ICHE6), the Code of Federal Regulations Title 21, and other applicable government regulations and Institutional research policies and procedures. All episodes of noncompliance will be documented.

The purpose of this active comparator study is to evaluate the effect of two different standard care approaches to anesthesia care for hip fracture surgery on recovery of ambulation at approximately 60 days (primary outcome) and other patient-centered outcomes measured at 365 days (plus or minus 60 days). The two approaches are spinal anesthesia (spinal block) and general anesthesia. Our overarching hypothesis is that patients undergoing hip fracture surgery with spinal anesthesia will demonstrate improved ambulation at approximately 60 days and better outcomes across a range of patient-centered endpoints compared to patients receiving general anesthesia.

1.1 Background and Relevant Literature

Hip fracture is a clinical condition that involves a break in the femur (hip bone) near where it attaches to the pelvis (Figure 1). Over 90% of hip fractures occur in individuals aged 50 or older, most commonly resulting from low-energy traumatic injuries, such as falls from standing in the context of established osteoporosis, chronic illness, or disability. Surgical treatment, via fixation of the fractured bone or partial or total replacement of the hip joint, is indicated for all types of hip fractures and approximately 95% of hip fracture patients undergo surgery.

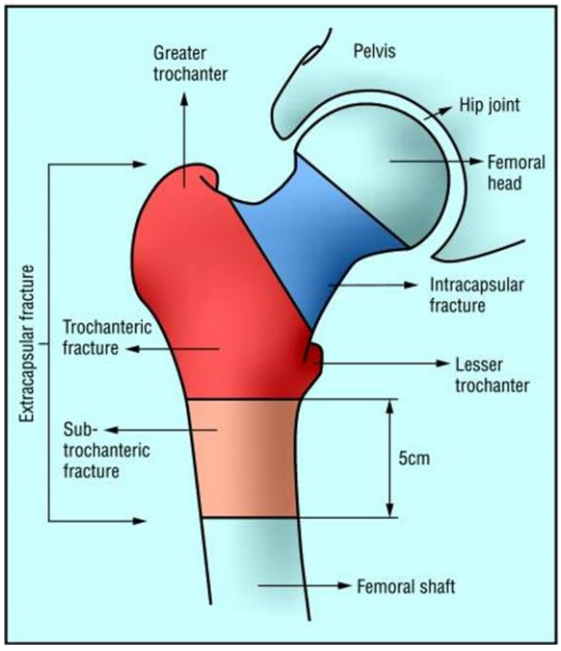

Figure 1: Locations of common hip fractures[1]

Hip fractures occur more than 300,000 times each year in the US and over 1.6 million times each year worldwide. Hip fractures carry major consequences for the individual and society.[6, 7] Within 12 months of fracture, 25% of patients die,[8, 9] and half of previously community-dwelling patients either die or require nursing home admission.[10] Among patients who survive to 12 months, 40% of those who could walk independently before fracture require human assistance to walk 10 feet.[11] Hip fractures create substantial needs for informal caregiving [12, 13] and post-acute and long-term care that carry major costs to society;[14] the estimated costs attributable to hip fractures in the US exceeded $12 Billion in 2005 and will exceed $18 Billion by 2025.[15] Moreover, the disability caused by hip fractures matters to older adults. In a study of patient views on hip fracture, 194 women aged 75 or older read hypothetical scenarios describing a "good" hip fracture after which they would continue to live independently, and a "bad" hip fracture that would require admission to a nursing home. *Of women surveyed, 80% stated that they would rather die than experience the loss of independence associated with a "bad" hip fracture.*[16]

No evidence-based interventions now exist to improve functional outcomes after hip fracture surgery beyond the immediate postoperative period.[17, 18] Nearly all hip fracture patients require orthopedic surgery and anesthesia,[19-21] making the anesthetic care episode a major opportunity to impact outcomes.[22]

Spinal and general anesthesia (defined below) represent the two standard care approaches to anesthesia for hip fracture surgery.[23] Basic and clinical research has identified multiple plausible mechanisms by

which spinal anesthesia may improve outcomes after hip fracture; nonetheless, major guidelines and systematic reviews have identified key evidence gaps [24-28] and anesthesia care for hip fracture varies markedly in practice.[29] While spinal and general anesthesia for hip fracture have been previously compared in retrospective studies and small randomized trials, much of the available prospective trial data is old and may not be reflective of current clinical practice.

REGAIN will be the first pragmatic multicenter prospective randomized trial of spinal versus general anesthesia for hip fracture surgery designed to evaluate the association of anesthesia technique with functional recovery after hip fracture. As such, it will fill critical evidence gaps to inform policy and practice.

1.2 Name and Description of the Interventions

We will compare two widely used approaches to anesthesia for hip fracture surgery.

General anesthesia uses injected or inhaled medications to keep people unconscious during surgery. Since general anesthesia depresses breathing and impairs protective airway reflexes, invasive airway interventions such as breathing tube placement and mechanical ventilation are usually required.[30]

Spinal anesthesia uses local anesthetic medications injected into the fluid surrounding the spinal cord to temporarily numb the legs and lower abdomen. Spinal anesthesia is the most widely used type of regional anesthesia for hip fracture surgery.[31, 32] While intravenous sedation is typically used for comfort with spinal anesthesia, invasive airway interventions are not typically required.[33]

1.2.1 Clinical Data to Date

Multiple clinical and laboratory studies provide evidence for physiologic effects of general and regional anesthesia that may plausibly lead to differences in important downstream patient-centered outcomes. These effects are summarized in **Figure 2.**

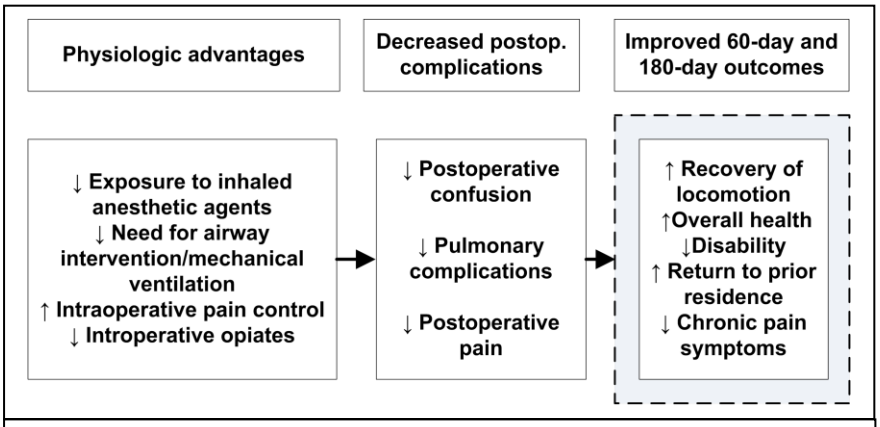

Figure 2: Proposed causal pathway linking spinal versus general anesthesia to improved patient-centered end-outcomes after hip fracture.

Pulmonary effects of general versus spinal anesthesia: General anesthesia negatively impacts lung function by impairing natural processes that prevent buildup of excess mucous,[34-36] keep individual lung units (alveoli) open,[37, 38] and maintain a normal breathing rate.[39-41] General anesthesia also impairs the function and coordination of muscles involved in breathing.[42, 43] In contrast, spinal anesthesia has minimal effects on lung function.[44-46] Compared to general anesthesia, spinal anesthesia is associated with higher blood oxygen levels after hip fracture surgery[47-49] and lower rates of postoperative pneumonia.[48, 50, 51] A recent large retrospective study by the PI found a lower odds of pulmonary complications with regional anesthesia among 18,159 patients undergoing hip fracture surgery (adjusted odds ratio (OR) 0.75, 95%CI 0.64 to 0.89).[52]

Effects on pain pathways: With general anesthesia, intravenous opiates like morphine are commonly used to treat pain; under-dosing of these drugs and inadequate pain control may lead to the development of long-term pain by sensitizing neurons that transmit pain signals to the brain ("central sensitization").[53-55] Spinal anesthesia prevents central sensitization by blocking transmission of pain signals at the level of the spinal cord, potentially contributing to better short- and long-term pain outcomes.[56-58]

Effects on cognition: General anesthesia impairs brain cell (neuron) function by influencing neuron gene transcription;[59, 60] signaling of impulses between neurons;[61-64] and systems that balance levels of important ions, such as calcium, within neurons.[65] General anesthesia has been shown to impair short- and long-term memory acquisition.[66-69] A 2004 meta-analysis of seven trials[47, 48, 50, 51, 70-72] found lower rates of postoperative confusion among patients who received spinal versus general anesthesia for hip fracture surgery (relative risk (RR), spinal versus general anesthesia: 0.50, 95% confidence interval (CI): 0.26 to 0.95).[26] Additionally, a large retrospective study suggested lower rates of cognitive impairment with spinal anesthesia at 6 and 12 months after hip fracture.[73]

Effects on patient-centered end-outcomes: Few prospective studies to date have examined differences in patient-centered end-outcomes with spinal versus general anesthesia for hip fracture surgery.

Mortality: A 2004 meta-analysis of eight small randomized trials of spinal versus general anesthesia for hip fracture observed a lower 30-day mortality with spinal anesthesia (RR 0.69, 95% CI: 0.50, 0.95).[26] Nonetheless, the randomized trials included in this meta-analysis have substantial limitations; many were completed prior to the 1990's, and may thus have limited relevance to current practice and the methodological quality of included trials was judged to be low overall.[25, 26] More recently, in a retrospective study of 18,159 hip fracture patients, the PI (Neuman) observed significant decreases in the adjusted odds of in-hospital mortality with spinal versus general anesthesia (OR: 0.71, 95% CI 0.54, 0.93),[52] although subsequent non-randomized analyses have yielded equivocal results regarding the association of anesthesia type with in-hospital[74] or 30-day mortality[29] differences. Importantly, even well-done non-randomized studies of anesthesia care for hip fracture patients are substantially limited by potential selection bias: since patients who receive regional anesthesia tend to be older and sicker than those who receive general anesthesia,[29, 52, 75] non-randomized studies will tend to underestimate any true benefits of spinal anesthesia.

Functional endpoints: To date, the association between anesthesia technique and functional endpoints has only been investigated in non-randomized studies. Historical cohort studies have shown inconsistent associations between anesthesia technique and locomotion after hip fracture.[76,73] As a pilot investigation for REGAIN, we conducted a retrospective (non-randomized) analysis of data collected in the FOCUS trial,[77, 78] a 47-center trial of transfusion management strategies in 2,016 hip fracture patients. While we found that patients who received spinal anesthesia were older than those who received general anesthesia (mean age 82.5 years vs. 80.9 years, P<0.001) they were slightly more likely to be alive and able to walk independently at 60 days (65.3% vs 64.9%) although this difference was not statistically significant (p=0.86).

Evidence gaps: Major gaps in evidence persist regarding the comparative effectiveness of common anesthesia options for hip fracture surgery. A 2011 systematic review by the UK Clinical Guideline Centre concluded that "no recent randomized trials were identified that fully address" the clinical effectiveness of regional versus general anesthesia for hip fracture surgery, and found that the available evidence "is old and does not reflect current practice."[25] The 2014 American Academy of Orthopedic Surgeons' guidelines for hip fracture care also note that available randomized studies are likely to be outdated and that "future research involving appropriately randomized patients may yet delineate which anesthesia technique is more appropriate in this patient population."[24]

2 Study Objectives

The purpose of the REGAIN trial is to evaluate the effect of two different standard care approaches to anesthesia for hip fracture surgery (spinal and general anesthesia) on recovery of ambulation at approximately 60 days (primary outcome) and other patient-centered outcomes measured at up to approximately 14 months (365 days plus or minus 60 days) after randomization. The overarching hypothesis of this study is that patients who receive spinal anesthesia will demonstrate improved ambulation at approximately 60 days and have better outcomes across a range of patient-centered endpoints compared to patients who receive general anesthesia.

2.1 Primary Objective

- To test the effect of spinal versus general anesthesia on recovery of ambulation at approximately 60 days after randomization.

2.2 Secondary Objectives

- To measure the impact of spinal versus general anesthesia on overall health and disability, cognition, return to the pre-fracture place of residence, pain, and mortality at approximately 60, 180, and 365 days after randomization.
- To assess the association of spinal versus general anesthesia for hip fracture surgery with in-hospital mortality, delirium, medical complications, and pain.
- To assess the association of spinal versus general anesthesia for hip fracture surgery with satisfaction with care.

3 Study Population and Duration of Participation

3.1 Inclusion Criteria

● Clinically or radiographically diagnosed intracapsular or extracapsular hip fracture
● Planned surgical treatment via hemiarthroplasty, total hip arthroplasty or appropriate fixation procedure
● Age ≥ 50 years
● Ability to walk 10 feet or across a room without human assistance before fracture

3.2 Exclusion Criteria

● Planned concurrent surgery not amenable to spinal anesthesia.
● Absolute contraindications to spinal anesthesia, including: (1) Known or suspected congenital or acquired coagulopathy; (2) active use of pharmacologic anticoagulants within a timeframe defined to contraindicate neuraxial block placement by available American Society of Regional Anesthesia guidelines;[79] (2) known or suspected unrepaired critical or severe aortic stenosis; (3) known or suspected active skin infection at the planned needle insertion site; (4) known or suspected elevated intracranial pressure contraindicating dural puncture.
● Patient is known or suspected to be at elevated risk for malignant hyperthermia
● Periprosthetic fracture
● Prior participation in the REGAIN trial
● Prisoner status
● Determination by the attending surgeon, the attending anesthesiologist, or the site Clinical Director or their designate, that the patient would not be suitable for randomization.

3.3 Subject Recruitment

Hip fracture is an acute condition requiring urgent hospitalization; as such, all subjects will be recruited in hospital settings between the time of presentation and the time of surgery. Orthopedic surgeons performing hip fracture surgery at each recruiting site will be contacted in advance of the initiation of study accrual to assess willingness to allow for patients to be enrolled. Patients under the care of non-participating orthopedic surgeons will not be recruited into this study. A list of non-participating orthopedic surgeons will be maintained by each site Clinical Director.

Site CRCs, Clinical Directors and other appropriate personnel will use multiple strategies to identify potentially eligible patients, potentially including interval calls to the hospital admissions office, specific hospital floors or units, relevant attendings, residents, or physician extenders (physician assistants or advanced practice nurses); reviews of inpatient census lists and operating room schedules; and requests

to physicians and physician extenders, emergency room personnel, ward clerks and floor nurses to contact site study staff when a hip fracture patient is admitted to the hospital.

For potentially eligible patients, the site CRC, site Clinical Director or other appropriately trained study staff member will approach the patient and/or their proxy between the time of diagnosis and the time of surgery to explain the study, complete a brief screening evaluation, and obtain informed consent. Alternately, members of the healthcare team may initially query patients or their proxies regarding potential interest in participation in the REGAIN trial; for interested patients or their proxies, the study team will be contacted to initiate recruitment and enrollment.

3.4 *Duration of Study Participation*

The planned maximum duration of study participation will be approximately 14 months from the date of randomization (i.e. 365 days plus or minus 60 days). Additional data on survival beyond this point may be obtained from administrative sources (e.g. NDI) where available.

3.5 Total Number of Subjects and Sites

Recruitment will end when approximately 2,424 subjects are enrolled. It is expected that this approximate number of subjects will be enrolled (i.e. informed consent for participation will be obtained) in order to produce approximately 1,600 randomized patients. This estimate is based on an assumption that one in three patients (33%) who undergo consent prior to surgery will be found to be ineligible for randomization on the day of surgery due to active clinical issues, timing of medication dosing, or clinical assessments by treating physicians or the site Clinical Director or their designate.

3.6 *Enrollment of children, pregnant women, fetuses, neonates, or prisoners:*

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

4 Investigational Plan

4.1 General Design

Randomized, multicenter, active comparator study of two alternative standard care approaches to anesthesia for hip fracture. Study endpoints will be assessed via in-person interview (during hospitalization), medical record review, telephone interview (after hospital discharge), and a vital records database search.

4.1.1 Screening Phase

Subjects will be screened in person by site CRCs, the site Clinical Director, or other designated study staff between the time of presentation and the time of surgery. Written informed consent and HIPAA authorization will be obtained in person from patients or their proxies (in cases where patients are unable to provide informed consent) by site CRCs, the site Clinical Director, or other designated study staff. A series of questions will be asked of patients or their proxies to determine if the potential subject is within the correct age range and to assess other inclusion and exclusion criteria. For potential subjects who may be eligible based on these criteria, written informed consent will be obtained from patients or (where necessary) their proxies.

Consenting patients will undergo an interview, to be carried out by site CRCs, the site Clinical Director, or other designated study staff, to collect necessary pre-randomization baseline data. Potentially eligible patients will undergo a final pre-randomization screening evaluation on the day of surgery to verify eligibility for randomization; since the assigned anesthesiologist is often not known before the day of surgery, and since changes in patient clinical status over time may impact eligibility, this evaluation will be required to occur on the day of surgery. Patients deemed eligible for study inclusion at this point will proceed to the study intervention phase.

4.1.2 Study Intervention Phase

For randomized patients, the intervention phase will comprise the period in which they are undergoing anesthesia care for hip fracture surgery. Prior to the start of anesthesia care, the treating anesthesiologist will be notified by the site Clinical Director, CRC, or other designated personnel, regarding the randomization status of the patient. As described below, patients will be randomized to one of two pragmatic treatment protocols that will instruct the treating anesthesiologist to deliver a standard care general anesthetic or a standard care spinal anesthetic. The study intervention phase will comprise the intraoperative anesthesia care episode, with the choice of primary anesthetic modality determined by this randomization assignment.

4.1.3 ***Follow Up Phase***

The follow up phase will extend from the end of the anesthesia care episode to up to approximately 14 months (i.e. 365 days +/- 60 days) after the date of randomization.

4.1.4 Allocation to Interventional Group

Participants will be randomly assigned to one of the two treatment regimens in a 1:1 ratio. Randomization will occur on the day of surgery via an automated algorithm constructed by the study Biostatistician. For each arm, balanced randomization of subjects, stratified by site, gender, and fracture type (intracapsular versus extracapsular), will be achieved by permuted block randomization with a variable block size.[80, 81] The randomization seed and actual algorithm will be kept by the study Biostatistician. Study procedures for randomization of subjects are detailed in Section 6.2.1 below.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Independence in walking at 60 days after randomization (Primary outcome). The primary outcome will be assessed by patient and/or proxy telephone interview at 60 days after randomization (+/- 30 days). Patients who report being unable to walk 10 feet or across a room without human assistance, or who die within 60 days of fracture will be classified as treatment failures; patients who require a cane or walker, but not human assistance, will not be classified as treatment failures, although data regarding the need for assistive devices will be collected for analysis as a secondary outcome. This outcome will also be assessed by telephone interview at 180 days (+/- 45 days) and at 365 days (+/- 60 days) where feasible for analysis as secondary study endpoints.

4.2.2 Secondary Study Endpoints

Overall health and disability. Overall health and disability will be assessed by in-person patient and/or proxy interview at baseline and by telephone interview at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization via the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0).[82] The WHODAS 2.0 is a patient-reported outcome that assesses cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society. It can be administered in person or by telephone in around 5 minutes.[83] The WHODAS 2.0 is scored on a scale from 0 (no disability) to 4 (extreme disability) for each of 12 items; item scores are summed to obtain a total score ranging from 0-48. The total score is divided by 48 and multiplied by 100 to convert it to a percentage of the maximum disability score; disability is classified as none (0-4%), mild (5-24%), moderate (25-49%), severe (50-95%) and complete (96-100%).[83, 84] The WHODAS has been validated across multiple conditions,[85-90] and has good criterion and convergent validity for assessing postoperative recovery at 3, and 6 months, with excellent responsiveness and internal consistency (Chronbach's Alpha > 0.90).[91]

Need for assistive devices for walking. The need for assistive devices for walking (e.g. cane, walker) will be assessed by in-person patient and/or proxy interview at baseline and by telephone interview at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization.

Ability to return home. All patients will be queried by telephone interview regarding location of residence at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization. For patients not residing in long-term nursing homes prior to fracture (93% of all U.S. hip fracture patients),[92] the percentage returning home at each time point will be assessed as a secondary outcome.

Chronic pain. Pain symptoms will be assessed by patient and/or proxy telephone interview at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization using the Numeric Rating Scale (NRS), by which pain symptoms are rated from 0 (no pain) to 10 (worst pain imaginable); pain items will assess the extent of pain at worst and on average over the past 24 hours, using similar wording to selected Brief Pain Inventory items.[93, 94]An additional item will query patients as to whether they are actively taking prescription medications for pain.

All-cause mortality. Vital status will be assessed via patient and/or proxy telephone interview at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization. Additionally, a National Death Index search will be performed in the final year of the study for all patients enrolled up to that point; studies evaluating NDI accuracy in determining mortality have reported rates of 83%-98%.[95, 96]

Cause of death. Cause of death will be determined via National Death Index search in the final year of the study for all patients enrolled up to that point.

Acute postoperative pain. Pain during hospitalization will be assessed by site CRCs or other appropriate staff via in-person patient and/or proxy interview before surgery and daily up to postoperative day 3 or the day of discharge (whichever occurs first) using a 0-10 Numeric Rating Scale; pain items will assess the extent of pain at worst and on average over the past 24 hours, using similar wording to selected Brief Pain Inventory items.[93, 94].

Satisfaction with care. Satisfaction with anesthesia care will be assessed by site CRCs or other appropriate staff via in-person interview on postoperative day 3 or the day of discharge (whichever occurs first) via the Bauer Patient Satisfaction Questionnaire,[97] as well as additional items assessing to undergo or recommend a similar anesthetic in the future.

Cognitive function. Cognitive function will be assessed via in-person interview at baseline, and via telephone interview via the Short Blessed Test (SBT), a well-validated brief cognitive screen appropriate for telephone administration at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization.[4, 98] The SBT is summarized in Table 1.

Postoperative delirium. We will assess patients for the presence of delirium via the 3D-CAM assessment tool via in-person interview at baseline and daily up to postoperative day 3 or the day of discharge (whichever occurs first). The 3D-CAM is a well-validated brief tool with high sensitivity and specificity for delirium.[99, 100]

Inpatient mortality and major inpatient morbidity. In-hospital mortality and other major intraoperative or postoperative complications will be assessed via chart review by site CRCs or other appropriate staff following hospital discharge, death, or at 30 days after randomization, whichever occurs first. We will assess the occurrence of major postoperative complications including but not limited to: (1) postoperative bleeding requiring transfusion; (2) myocardial infarction; (3) congestive heart failure; (3) stroke or transient ischemic attack; (4) pneumonia; (5) urinary tract infection; (6) wound infection; (7) thromboembolic complications; (8) unplanned intubation; (9) prolonged mechanical ventilation; (10) acute renal failure; (11) cardiac arrest requiring CPR or defibrillation; (12) return to the operating room. Complication definitions for use in REGAIN will adapt standard definitions, such as those used by the National Surgical Quality Improvement Program.[101]

Table 1: Short Blessed Test of orientation, memory, and concentration[4]			
Item	Max. # of errors	Weight	Maximum score (errors x weight)
1. What *year* is it now?	1	4	4
2. What *month* is it now?	1	3	3
Memory phrase: Repeat this phrase after me: John Brown, 42 Market Street, Chicago	N/A	N/A	N/A
3. About what *time* is it? (within 1 hour)	1	3	3
4. *Count* backwards from 20 to 1	2	2	4
5. Say the months of the year in reverse order.	2	2	4
6. Repeat the memory phrase.	5	2	10
Maximum total score			28
To score the SBT, the interviewer records the number of errors on each item up to the maximum number of errors allowed for each item. The number of errors on each item is multiplied by that item's weighting factor to obtain the item score. Item scores are summed to obtain a total score between 0 and 28. Scores of 0-4 indicate normal cognition; scores of 5-9 indicate impairment consistent with early dementia; and scores of 10 or more indicate impairment consistent with dementia.[5]			

4.2.3 Primary Safety Endpoints

Spinal anesthesia and general anesthesia are standard care approaches with longstanding track records of safety in appropriately selected patients. The primary safety evaluation will assess whether the adverse event profile associated with participation in the REGAIN trial differs meaningfully from the adverse event profile that could be expected with spinal and general anesthesia for hip fracture surgery in typical clinical practice. We will collect data on the following known or established potential risks of spinal and/or general anesthesia:

- Intraoperative cardiac arrest requiring CPR caused by anesthetic medications or techniques
- Malignant hyperthermia requiring dantrolene or intraoperative anaphylaxis caused by medications used to induce or maintain general or spinal anesthesia
- Intraoperative aspiration resulting in aspiration pneumonia or aspiration pneumonitis
- Epidural hematoma requiring surgical intervention occurring within 24 hours of spinal anesthesia
- Paralysis of the lower extremities lasting greater than 24 hours following spinal anesthesia
- Fall within 12 hours of anesthesia care
- Unplanned postoperative mechanical ventilation lasting greater than 6 hours in a patient not previously requiring mechanical ventilation

These endpoints will be assessed via medical record review for the first 3 postoperative days and at the time of discharge; for patients discharged prior to postoperative day 3, these endpoints will be assessed through the day of discharge.

5 Study Intervention

5.1 Description

Patients will be randomized to receive standard care spinal anesthesia or standard care general anesthesia. The administration of anesthesia will be carried out in the course of routine care by practicing anesthesiologists, residents, nurse anesthetists and other appropriately trained and credentialed clinical staff at each study site. Prior to study initiation, anesthesia staff will be queried by the site Clinical Director regarding their willingness to participate in the study and non-participating anesthesia staff will be identified by the Clinical Director. Additionally, Clinical Directors will identify anesthesia staff who are eligible to provide care for study cases; experience- or skill-based standards for anesthesiologist participation in the REGAIN trial will be determined locally based on the judgment of the site Clinical Director and other study staff. As anesthesia care for patients enrolled in the REGAIN trial will be delivered by participating anesthesiologists as a part of their routine job function, participating anesthesiologists will not be considered part of the study team unless involved in other aspects of the REGAIN trial. Patients who will be under the care of anesthesia staff at the time of induction of anesthesia who are unwilling to participate in REGAIN or who the site Clinical Director has determined to be ineligible for participation in REGAIN will be excluded from randomization.

The intervention will occur by providing the assigned clinical anesthesia staff instructions directing them to perform a standard care spinal anesthetic or a standard care general anesthetic (below). These regimens use standard terminology and do not require specialized techniques, drugs, or monitors beyond those available and in common use in standard care settings. All participating anesthesia staff will undergo a brief orientation to the protocol by the site Clinical Director; instructions will be provided that all aspects of anesthesia care within the protocol should adhere to national, local, and individual standards of practice for the provision of spinal or general anesthesia, including but not limited to: the location of block administration (OR vs. designated block room); medication selection and dosing; decisions to convert from spinal to general anesthesia; postoperative analgesia; and decisions regarding the appropriate duration and number of attempts permitted to perform a spinal anesthetic or to induce general anesthesia.

5.2 Intervention Regimen

At the time of randomization, providers will receive instructions regarding anesthesia care similar to the statements shown below, allowing for minor wording changes or revisions for clarity.

Provider instructions:

Treatment arm 1 (spinal anesthesia): *Please perform a single-shot spinal anesthetic, with sedation as needed for block placement and intraoperative comfort. Please titrate any intraoperative sedation to maintain arousability to tactile stimulus or voice. Conversion to general anesthesia is permitted if required by clinical circumstances. Please conduct all other aspects of anesthesia care, including monitoring, medication selection and dosing, supplemental nerve blocks, and management of intraoperative events as per your usual routine.*

Table 2: Observer's Assessment of Alertness/Sedation[2, 3]

Score	Subject responsiveness	Sedation level
5	Responds readily to name spoken in normal tone	Alert
4	Lethargic response to name spoken in normal tone	Light sedation
3	Responds only after name is called loudly and/or repeatedly	Moderate sedation
2	Responds only after mild prodding or shaking	Moderate sedation
1	Does not respond to mild prodding or shaking	Deep sedation

For patients randomized to receive spinal anesthesia, treating anesthesiologists will receive instructions to document the level of sedation based on the Observer's Assessment of Alertness/Sedation Scale (OAAS), a simple, validated measure of alertness among sedated subjects.[2, 3] The OAAS scoring system to be used in the REGAIN trial appears in Table 2.

Provider instructions: Treatment arm 2 (general anesthesia): *Please perform a general anesthetic. Please use an inhaled anesthetic agent for maintenance and use intravenous opiates as needed for analgesia. Airway management may be via endotracheal tube, laryngeal mask airway, or other device as dictated by clinical circumstances. Please conduct all other aspects of anesthesia care, including monitoring, medication selection and dosing, supplemental nerve blocks and management of intraoperative events as per your usual routine.*

5.3 Blinding

Due to the nature of the study intervention, it will not be possible to blind patients or treating providers (anesthesiologists or surgeons) to treatment assignment.
As permitted by staff availability and site resources, we will encourage site staff to perform the postoperative day 1-3 3D-CAM assessments in a blinded fashion by having these assessments performed by an individual other than the team member(s) who are responsible for obtaining the randomization assignment (see Section 6.2.1, "Randomization") and conducting chart reviews for adverse safety events. Additionally, where appropriate, patients will be instructed to not inform the 3D-CAM assessor of the type of anesthesia they received. If this is not possible based on staff availability or site resources, we will not require blinded collection of in-hospital outcomes data.

Post-discharge outcomes, including the primary study outcome, will be assessed by centrally by telephone. Telephone follow-up for post-discharge outcomes assessment will be carried out by University of Pennsylvania CCC staff who will be blinded to treatment assignment.

Assessments of aggregate data related to patient characteristics and study outcomes will occur in a blinded fashion such that investigators cannot determine subject randomization assignment; unblinding at the level of the individual patient will be permitted as needed for making determinations of relatedness for adverse events (see section 8.3 below). Unblinding procedures for the overall study are described below in section 8.5 below.

5.4 Subject Compliance Monitoring

The PI and/or CCC staff will assess the type of anesthesia actually received via retrospective chart review, to be completed by site CRCs or other study personnel following death, hospital discharge, or postoperative day 30, whichever comes first. While the type of anesthesia received will be investigated to assess for the extent of crossover between study arms, such crossover will not be considered to represent protocol non-compliance, since treatment regimens permit deviations from assigned treatments based on clinical rationale. Similarly, for patients randomized to spinal anesthesia, sedation beyond arousability to voice or tactile stimulus will not be considered to represent non-compliance, since study protocols allow for provider selection and dosing of sedation based on clinical rationale.

To assess study performance, data on anesthesia care will be reviewed for each recruiting site after the first 10 subjects at each site are randomized. Further site-level analyses as to assess safety events and protocol implementation will be performed on an as-needed basis.

6 Study Procedures

6.1 Screening phase

6.1.1. Initial screening visit

The initial screening visit will be carried out by site CRCs or other appropriate staff between the time of presentation and the time of surgery. It will involve a patient and/or proxy interview and medical record review to assess inclusion and exclusion criteria. Data will be recorded on the Initial Screening Visit Form and entered into the online DMS. Written informed consent will be obtained at this visit and documented in the medical record. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *Informed Consent*
- *HIPAA Authorization*
- *Screening interview (Age; ability to walk 10 feet without assistance prior to fracture; receipt of selected anticoagulant or antiplatelet medications; information on malignant hyperthermia risk; gender, ethnicity, and race)*
- *Medical record review (Planned surgical procedures; history of critical or severe aortic stenosis, elevated intracranial pressure, or lumbar skin infection; available laboratory data on platelets, INR and PTT)*

6.1.2. Baseline data collection visit

The baseline data collection visit will be carried out by site CRCs or other appropriate staff between the time of presentation and the time of surgery. It will involve a patient or proxy interview and medical record review to assess relevant pre-fracture and pre-randomization covariates. Data will be recorded on the Baseline Data Collection Visit Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

Data will also be collected at this visit regarding patient and proxy contact information as needed to facilitate subsequent telephone follow-up; patient social security number and Medicare number as

needed to facilitate data linkages to the NDI and Medicare claims; and names and contact numbers of two additional contacts who do not live with the patient who may be available to facilitate follow-up in the event that we are unable to reach the patient. While information on alternative contact individuals will be collected from patients to assist with follow-up, availability of an alternative contact is not a requirement for participation in the REGAIN trial. Contact data will be stored on the Patient Contact Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use. Forms including patient contact information will be stored separately from all other CRFs.

- *Medical history interview and medical record review (Date of birth; comorbidities; height; weight; do-not-resuscitate status; most recent available heart rate, blood pressure, and oxygen saturation values; fracture location and laterality; supplemental oxygen or mechanical ventilation; most recent available serum creatinine; pre-fracture pain medication use)*
- *Pre-fracture ambulation independence questionnaire*
- *Pre-fracture residential status assessment (i.e. residence at home, in a nursing home, etc…)*
- *Short Blessed Test (cognition)*
- *3D-CAM (delirium)*
- *WHODAS 2.0 (overall health and disability prior to fracture)*
- *Pain symptom questionnaire (average and worst pain over past 24 hours; pain prior to hip fracture)*
- *Brief Resilience Scale (resilience to adversity)*
- *Patient, proxy, and secondary contact information (Patient/proxy telephone numbers, addresses, e-mails; patient social security number and Medicare number; names, telephone numbers, and home addresses of two additional contacts not living with the patient to facilitate follow-up.)*

6.1.3. Day of surgery screening visit

The day of surgery screening visit will be carried out by site CRCs or other appropriate staff on the day of surgery and will involve a medical record review and an interview with treating physicians to assess patient appropriateness for randomization. Patients with identified contraindications to spinal anesthesia will be excluded prior to randomization. Data will be recorded on the Day of Surgery Screening Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *Medical record review (Receipt of selected anticoagulant or antiplatelet medications; available laboratory data on platelets, INR and PTT)*
- *Physician verification of eligibility*

6.2 Study Intervention Phase

6.2.1 Randomization

Randomization will be carried out on the day of surgery; randomization will be performed centrally through the study electronic DMS. The site CRC, Clinical Director or other study staff will obtain the randomization assignment electronically from the DMS and will communicate the treatment assignment to the anesthesia team on the day of surgery verbally in person or by telephone, e-mail, text, or other appropriate modality. Designated alternate study personnel who can access the randomization assignment will be identified by the PI and the site Clinical Director to serve as a backup in the event that the site Clinical Director is not available. In the event that the DMS is not available or cannot be accessed by study personnel, the randomization assignment will be communicated to appropriate site personnel by directly by the PI or designated CCC or DCC staff.

6.2.2 Intraoperative phase

All intraoperative care will be carried out by practicing clinicians at the study site.

- *Standard care spinal anesthesia or standard care general anesthesia*

- *Measurement of sedation level via OAAS scale*
- *Monitoring, clinical management, and additional anesthesia procedures as dictated by standard care*

6.3 Follow Up Phase

6.3.1 Postoperative day 1 and 2 visits

Patients will be visited on the first and second postoperative days by site CRCs or other study personnel to complete an in-person interview to assess delirium and pain. Data will be recorded onto the Postoperative Day 1 and 2 Visit Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *3D-CAM assessment (delirium)*
- *Pain symptom questionnaire (average and worst pain over past 24 hours)*
- *Postoperative mortality assessment*

6.3.2 Postoperative day 3 visit

Patients will be visited on the third postoperative days by site CRCs or other study personnel to complete an in-person interview to assess delirium, pain, and satisfaction with anesthesia. Data will be recorded onto the Postoperative Day 3 Visit Form and entered into the online DMS. For patients discharged on postoperative day 1 or 2, this interview will be completed on the day of discharge in lieu of the postoperative day 1 or 2 interview described above. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *3D-CAM assessment (delirium)*
- *Pain symptom questionnaire (average and worst pain over past 24 hours)*
- *Postoperative mortality assessment*
- *Anesthesia satisfaction questionnaire (satisfaction with anesthesia care)*

6.3.3 Post-discharge medical record review

Site CRCs will complete a detailed chart abstraction to assess intraoperative events and major postoperative adverse events occurring up to the date of discharge, death, or at postoperative day 30, whichever comes first. Chart abstractions will take place following discharge, death, or postoperative day 30 within a timeframe to be determined by the PI and site personnel. Data will be recorded on the Medical Record Review Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

For each participating site, CCC staff at the University of Pennsylvania will over-read and re-abstract chart data for the first 3 randomized patients and additional charts as needed, as determined by the results of the initial chart review; for sites other than the University of Pennsylvania, charts will be photocopied and mailed via certified mail to the CCC. Data will be re-abstracted by CCC staff and entered into the DMS for comparison to the chart abstraction results from individual sites. Following abstraction, photocopied charts will be disposed of in a locked cabinet and shredded. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *Medical record review (Date of surgery; anesthesia and surgery start and stop times; surgical procedure performed; intraoperative data including but not limited to estimated blood loss; fluids and blood products administered in the OR; intraoperative blood pressure and oxygen saturation; ASA physical status classification; initial anesthetic type; intrathecal agents administered (for patients receiving spinal anesthesia); documented level of arousability; peripheral nerve blocks performed; benzodiazepines and intravenous opioids administered in the OR; intraoperative adverse events including but not limited to cardiac arrest requiring CPR, anaphylaxis, aspiration; postoperative adverse events including but not limited to bleeding requiring transfusion; myocardial infarction, congestive heart failure, stroke or transient ischemic attack, pneumonia,*

urinary tract infection, wound infection, thromboembolic complications, unplanned intubation, prolonged mechanical ventilation, acute renal failure, cardiac arrest requiring CPR or defibrillation, epidural hematoma requiring surgical intervention, new permanent paralysis of the lower extremities, return to the operating room, inpatient falls, unplanned postoperative mechanical ventilation; additional surgeries performed; ICU utilization discharge destination; date of first ambulation; discharge status.)

Where relevant, data will also be abstracted from the chart regarding the timing and/or severity of specific complications or events, as well as causes of specific events as documented in the medical record.

6.3.4 60-day, 180-day, and 365-day interviews

Interviews for all patients will occur at approximately 60 days, 180 days, and 365 days after randomization. Interviews will be conducted centrally via telephone by trained CCC staff overseen by the study PI.

CCC staff will call patients and/or proxies using contact information obtained at the time of the baseline interview within the following assessment windows: between 30 and 90 days after randomization (for the 60-day interview); between 135 and 225 days after randomization (for the 180-day interview); and between 305 and 425 days after randomization (for the 365 day interview). The listings of patients due for follow-up will be generated by the study DCC and will be provided by the DCC to CCC personnel.

Patients or their proxies will complete a structured telephone interview. Additionally, where patients are providing their own responses to interview items, we will also conduct a brief interview with a proxy respondent (if available) during the same call to verify the patient's response regarding the primary outcome (i.e. degree of independence in ambulation).

Participants who are unavailable at the time of the initial attempted contact will receive follow-up calls up to five to seven times weekly at variable times over the course of the assessment window; for non-respondents, CCC staff will place calls to secondary contacts and reminders will be sent via secure e-mail and registered mail where feasible to minimize loss to follow-up. For patients who cannot be reached within the assessment window for a particular interview, a letter approved by the IRB may be sent to the patient's and proxy's address providing CCC contact information and requesting phone contact with the patient and/or the proxy with a recommended window of contact. This process will be repeated once every 30 days until either contact is made, a total of 4 letters are sent, or 425 days have passed since the date of randomization. All letters will be sent using a method that confirms delivery, either United States Postal Service, FedEx, or a similar carrier. Choice of carrier will be at the discretion of the PI.

Calls will be made during business and evening hours of the patient's residence. Where feasible, calls will be audio-recorded with permission for quality assurance; audio files will be kept in digital format on media that will be stored in secure, locked cabinets within offices controlled by the PI when not in use. Audio files will be accessed for random auditing of interviews and additionally as needed for quality control by the study PI and CCC staff. When possible, the results of the follow-up interviews will be entered directly into the electronic study DMS via the 60, 180, and 365 Day Follow-up Forms and the 60 Day Proxy Interview for the Primary Outcome Form. Hard copy forms will be used in the event that study staff are unable to access the online DMS; data will be abstracted from hard copy forms by study staff into the online DMS and stored in secure locked cabinets within offices that are controlled by study personnel and locked when not in use.

- *Ambulation independence questionnaire*
- *Proxy ambulation independence questionnaire.*
- *Pain symptom questionnaire (pain with ambulation and at rest; pain medication usage)*
- *Mortality assessment*
- *Residential status assessment (i.e. residence at home, in a nursing home, etc…)*
- *WHODAS 2.0 (overall health and disability)*
- *Short Blessed Test (cognition)*

6.3.5 National death index search

A National Death Index (NDI) search will be performed during the final year of the study to obtain survival and cause-of-death data on all patients enrolled up to that point. The following patient-level variables will be submitted to the NDI to complete this search where available: first and last name, middle initial, social security number (complete or last 4 digits), month, day, and year of birth, race, sex, and state of residence. These data will be mailed to the NDI on an encrypted, password-protected CD-ROM or other appropriate digital media via certified overnight mail. No more than one individual will have access to transmitted data, and all transmitted patient-level data will be destroyed following the completion of the NDI search; no patient-level data will be retained at the CDC following completion of the NDI search.

NDI data will be transmitted from the US CDC's National Center for Health Statistics via password-protected encrypted CD-ROM or similar media to the CRCU or the CCC or DCC PI via overnight mail, and will be transferred directly to the DMS by CRCU staff. Following data transfer, the original NDI disk will be stored. Hard copy forms will be stored in a secure locked cabinet within offices controlled by study personnel and locked when not in use.

- *All-cause mortality*
- *Cause of death*

6.3.6 Medicare claims linkage

Permission will be sought from randomized patients who are Medicare beneficiaries to perform linkage of study data to Medicare claims once such claims are available and additional funding can be secured. Funding from the present grant will not be used to fund this linkage or related analyses; methods for data linkage, data management and analysis will be governed by a separate protocol.

6.3.7 End of Study Interview

Either the 180 day interview or the 365 day interview may represent the end of study interview depending on the timing of enrollment into the REGAIN trial and the availability of funding at the time of the scheduled interview.

6.4 Rescue Therapy

Management of all intraoperative events will be at the discretion of the treating anesthesiologist and surgeon based on clinical expertise and standard care.

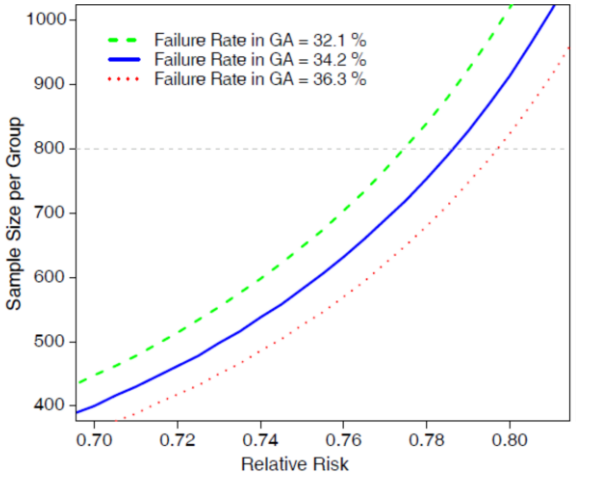

Figure 3. Sample sizes required for 80% power to detect a difference in the primary endpoint for patients randomized to spinal vs general anesthesia across a range of effect sizes.

6.5 Unscheduled Visits

No unscheduled visits will take place over the course of the study.

6.6 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the site Clinical Director for lack of adherence to study procedures or visit schedules, AEs, due to family preferences, or at the discretion of the treating physician. The site Clinical Director may also withdraw subjects for administrative reasons. The date of withdrawal and any known reasons for withdrawal will be documented on the Subject Withdrawal Form and entered into the online study DMS.

6.6.1 Data Collection and Follow-up for Withdrawn Subjects

No attempts will be made to collect additional follow-up data from participants who have withdrawn consent.

7 Statistical Plan

Statistical analyses using datasets including identifiable patient data will be carried out on secure servers maintained by the Penn Clinical Research Computing Unit (see below); analyses will use standard statistical software such as R, SAS, and Stata.

7.1 Primary Endpoint

The primary endpoint for this study will be death or inability to walk 10 feet or across a room without human assistance at approximately 60 days after randomization. This endpoint will be analyzed as a binary outcome.

7.2 Secondary Endpoints

Secondary endpoints include both binary and continuous outcomes and will include but not be limited to:

- Inability to walk 10 feet or across a room without human assistance at 180 and 365 days
- Mortality (in-hospital, 60-day, 180-day, 365-day)
- Need for assistive devices for ambulation (60-day, 180-day, 365-day)
- All cause mortality (via NDI search)
- Cause of death (via NDI search)
- SBT score (60-day, 180-day, 365-day)
- WHODAS 2.0 score (60-day, 180-day, 365-day)
- Pain scores at rest and with movement (in-hospital, 60-day, 180-day, 365-day)
- New utilization of prescription pain medications (in-hospital, 60-day, 180-day, 365 day)
- Satisfaction with anesthesia care (in-hospital)
- Delirium (in-hospital), including presence of delirium and delirium severity score
- Major postoperative morbidity, including selected inpatient adverse events (in-hospital)

7.3 Sample Size and Power Determination

Power and sample size. Our sample size calculation is based on the primary outcome (inability to walk or death at 60 days). **Figure 3** shows sample size requirements for 80% power to detect a range of relative risks for this outcome between two randomized arms (α=0.05). The middle line shows the sample sizes required assuming a 34.2% rate of the primary outcome in the general anesthesia arm, (the rate observed in the 2,100-patient FOCUS trial);[78] the upper and lower lines show required sample sizes based on the FOCUS 95% confidence limits for this outcome (i.e., 32.1% and 36.3%). Our calculations assume a 5% loss to follow-up and a 5% crossover rate from spinal to general anesthesia.[102, 103]

Assuming that the primary outcome occurs in 34.2% of general anesthesia patients our planned sample will provide **80% power to detect a relative risk of 0.78** for this outcome among patients receiving spinal versus general anesthesia and **90% power to detect a relative risk of 0.76**. These effect sizes fall within the 95% confidence intervals for the effect of regional anesthesia on in-hospital mortality, pulmonary complications and postoperative confusion seen in prior retrospective studies[29, 52] and randomized trials,[26] and are of sufficient magnitude to justify changes in practice and policy; while smaller differences could exist, effects below this level would be unlikely by themselves to justify large-scale changes in anesthesia care. Additional power calculations indicate that the planned sample will have adequate power to detect clinically meaningful differences in secondary study endpoints, including survival, delirium, pain, overall health and disability, and changes in cognitive status over time.

7.4 Statistical Methods

7.4.1 Baseline Data

The distributions of analysis variables will be examined using tabular and graphical methods, such as histograms and boxplots, to identify outliers that may represent errors not captured by automated processes. Such values will be verified or corrected prior to analysis. Measures will be summarized using appropriate descriptive statistics, including means and standard deviations, medians, ranges, and proportions. Analyses will use commercial computing packages including SAS, Stata, and R.

7.4.2 Efficacy Analysis

All hypothesis tests will use a two-sided significance level (Type I error) of $\alpha = 0.05$. As the primary outcome (inability to walk or death at approximately 60 days) is binary, the primary analysis will compare the proportions of patients meeting this outcome between groups randomized to spinal versus general anesthesia using chi-square tests, stratified by site, gender, and fracture type. Secondary analyses will use multivariable logistic regression models to control for other covariates such as age, race, and baseline WHODAS 2.0 score. Similar approaches will be used to evaluate binary secondary outcomes, including mortality at approximately 180 and 365 days, return to the prior residence at approximately 180 and 365 days, occurrence of any major in-hospital complication, and binary pain, health/disability, and satisfaction endpoints.

For continuous endpoints such as overall WHODAS 2.0 score we will use analysis of variance (ANOVA) adjusted for age, gender, and fracture type. Further adjusted analysis will be performed using linear regression adjusting for potential covariate effects; normalization transformation may be considered if the normality assumption is violated. Standard regression diagnostics, including residual plots, and influence statistics will be used to identify outliers and examine the assumptions. We will provide in the analyses, in addition to tests of significance, confidence intervals for treatment effect, and various approaches to assess the robustness of the estimates to nuisance factors. (IR-6) Other continuous endpoints such as pain and satisfaction scores will be analyzed using similar methods.

Heterogeneity of Treatment Effects (HTE). For the primary outcome, analyses of treatment effects within pre-specified subgroups defined by: (1) fracture type; (2) gender; (3) pre-fracture level of overall disability; (4) pre-fracture disability in locomotion; (5) age category; (6) baseline cognitive status; (7) surgical procedure; (8) baseline pulmonary disease; (9) baseline cardiac disease; (10) nursing home versus non-nursing home residence prior to fracture. Subgroup comparisons will be conducted if any treatment-covariate interactions are at least suggestive ($p<0.20$; HT-3) and sample sizes and numbers of events within these subgroups are sufficient for analysis. Secondary outcomes also will be assessed for HTE. If there is a treatment difference together with evidence of heterogeneity, the relevant covariates and interactions will be added to the relevant regression models to see if an overall difference still exists. Additional pre-specified subgroup analyses will be performed for in-hospital delirium outcomes among patients for whom assessors were and were not blinded to treatment assignment.

7.4.3 Interim Analysis

As discussed in Section 8.6 below (“Stopping Rules”), we do not plan to perform interim analyses to test for superiority or inferiority of either study regimen with regard to any of the primary or secondary study outcomes.

7.4.4 Safety Analysis

Randomized subjects will have information collected on defined safety endpoints as described above in Section 4.2.3. (“Primary Safety Endpoints”) The overall study safety analysis will assess the rate of all combined safety as well as the rates of individual safety events. Reviews of safety data will be performed after the enrollment of the first 100 patients, and after accrual of 25%, 50%, and 75% of the study sample.

Reviews of safety data will be carried out by the DSMB, the PI, and other appropriate CCC and DCC leadership.

7.5 Subject Population(s) for Analysis

- All-randomized population: The main analysis for the primary outcome will include the all-randomized population; this population will also be used for the main analysis of selected secondary outcomes including mortality, major intraoperative and postoperative adverse events, WHODAS 2.0 score, SBT score, pain at motion and at rest, satisfaction with care, location of residence, and severity of delirium as assessed by 3D-CAM.
- Per-protocol population: Secondary analyses for all of the above named-variables will restrict the population under consideration to patients who received the initial anesthesia type (i.e. spinal or general anesthesia) to which they were randomized
- Randomized patients without delirium at baseline: Patients for whom delirium is present prior to randomization will not be eligible for inclusion in analyses that examine a binary endpoint indicating the presence or absence of new postoperative delirium. As such, this analysis will include randomized patients without a baseline diagnosis of delirium prior to randomization.
- Randomized patients living at home prior to fracture: Patients not living at home prior to fracture will not be eligible for inclusion in analyses that examine the percentage returning to home at 60, 180, and 365 days. As such, this analysis will include only randomized patients living at home prior to fracture.
- Randomized patients not requiring assistive devices for ambulation at baseline: Patients for whom assistive devices were required for ambulation prior to fracture will not be eligible for inclusion in analyses that examine binary endpoints indicating whether such devices are required for ambulation after fracture. As such, this analysis will include randomized patients without a requirement for assistive devices for ambulation prior to fracture.
- Randomized patients without cognitive dysfunction at baseline: Patients for whom cognitive dysfunction is present prior to randomization will not be eligible for inclusion in analyses that examine a binary endpoint indicating the presence or absence of new cognitive dysfunction at 60, 180, or 365 days. As such, this analysis will include randomized patients without cognitive dysfunction, as defined by SBT score, prior to randomization.
- Randomized patients not requiring prescription pain medicines at baseline: Patients for whom prescription pain medicines are required for pain control prior to fracture will not be eligible for inclusion in analyses that examine a binary endpoint indicating the presence or absence of new need for prescription pain medicines at 60, 180, or 365 days. As such, this analysis will exclude randomized patients reporting use of prescription pain medicines prior to fracture.
- Additional outcome-specific subpopulations: Additional sub-populations will be defined at the time of analysis as required for appropriate secondary analysis of key study endpoints.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events.

8.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal

- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious will be regarded as **non-serious adverse events**.

8.2 Recording of Adverse Events

At each contact with the subject and at the time of hospital discharge, study personnel will seek information on adverse events by specific questioning and, as appropriate, by examination and medical record review. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events identified during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be determined by an adverse event review committee as being definitely related, probably related, possibly related, unlikely to be related or unrelated to the study intervention or other study procedures. For purposes of making determinations of relatedness, members of the safety monitoring committee may have access as needed to relevant intraoperative, preoperative, and postoperative data; additional identifying data not required for determinations of relatedness will be suppressed. If needed for determinations of relatedness, unblinding with regards to treatment assignment will be permitted at the level of the individual case. The safety monitoring committee will include 2-3 members and will be led by the PI or their designate.

8.4 Reporting of Adverse Events and Unanticipated Problems

At each contact with each subject, the study staff will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in appropriate case report forms. All clearly related signs, symptoms, and abnormal diagnostic procedure results will be documented.

Initial reports will be submitted as narratives to the PI office; the minimum necessary information to be provided at the time of the initial report will include:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies.

8.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the site Clinical Director's or PI's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The Clinical Director will be responsible for ensuring that all SAE are followed until either resolved or stable.

8.4.2 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to the Clinical Coordinating Center by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the site Clinical Director and submitted to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and/or email to:

Mark David Neuman, M.D., M.Sc.
Study Director, REGAIN Trial
University of Pennsylvania
308 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104
Office: (215) 746-7468
Cell: (215) 760-7471
Email: mark.neuman@uphs.upenn.edu

Within the following 48 hours, the site Clinical Director will provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This will include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events will be provided promptly to the study sponsor.

8.4.3 Investigator Reporting: Notifying the IRB

Reports of the following problems will be reported to the Penn IRB and other appropriate site IRBs within 10 working days from the time the investigator becomes aware of the event:

Any adverse event that occurs any time during or after the research study, which in the opinion of the principal investigator is:

- **Unexpected** (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

- **Related** to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

The above is required regardless of whether the event is serious or non-serious, on-site or off-site.

Protocol Deviations
Any protocol deviations initiated without Sponsor and/or Penn IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, will be reported to the Sponsor and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

Reporting Process
Unanticipated problems as defined above will be reported to the Penn IRB using the appropriate CRF or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the PI's office.

Other Reportable events:
The following events will also be reported to the Penn IRB:

- Any adverse event that would cause the modification of the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency, such as:
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.4.4 Sponsor reporting: Notifying participating investigators

Investigators at participating sites will be notified by the CCC of any of the above adverse events or findings to participating investigators based on the same timing as required for IRB reporting described above.

8.5 Unblinding Procedures

Where feasible based on staff availability and site resources, some sites may conduct blinded assessments for in-hospital outcomes. As at least one study team member at each site will be unblinded to treatment assignment, no unblinding procedures are proposed for the REGAIN trial at the level of the individual site.

Assessments of aggregate data related to patient characteristics and study outcomes will occur in a blinded fashion such that investigators cannot determine subject randomization assignment; unblinding at the level of the individual patient will be permitted as needed for making determinations of relatedness for adverse events (see section 8.3 above). Unblinding with regard to randomization assignment for the full study sample will occur at the end of study enrollment, or prior to that point as per the determination of the Principal Investigator based on the input of the DSMB and/or the study sponsor.

8.6 Stopping Rules

Spinal and general anesthesia are universally accepted as standard care practices for hip fracture surgery. There is no known or expected difference in overall risk or safety to patients between these two approaches. For this reason, we do not propose formal stopping rules based on demonstrated superiority or inferiority of either treatment with regard to the primary or secondary endpoints.

8.7 Medical Monitoring

The site Clinical Director will oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

8.7.1 Data and Safety Monitoring Plan

Data and safety monitoring will be the responsibility of the Study Director/PI (Neuman), the study Biostatistician, site Clinical Directors, and a Data Safety Monitoring Board (DSMB).

Data Safety Monitoring Board
The DSMB roles, responsibilities, and operating procedures are defined by the REGAIN DSMB Charter; this charter will be initially drafted by the REGAIN CCC and DCC leads and will be modified and ratified by the DSMB prior to the initiation of subject recruitment. The DSMB will be composed of 5-7 patients, physicians, and investigators who are not involved in the conduct of the study in any way; who do not have subordinate relationships with the PI or any member of the study team; and who are qualified through other experience or training to review the clinical and research data from the study. The selection of the DSMB according to these criteria will enable the protection of subjects and the integrity of the data through a group which is sufficiently objective yet clinically qualified to fulfill the role. The DSMB will be unblinded to subject treatment assignment.

DSMB Standard Operating Procedures
The DSMB will be identified by the PI (Neuman), the Biostatistician, and/or the funding sponsor, and will be invited to serve in this capacity until the conclusion of the study. The DSMB will meet prior to the initiation of enrollment to review the protocol, the DSMB charter and reporting templates. Subsequent DSMB meetings will review the protocol, safety and adverse event data, available outcome data, and information on subject accrual and protocol compliance; these meetings will take place within 1 month of the time of planned interim safety event analyses, which will occur after randomization of the first 100 patients and after randomization of ¼, ½, and ¾ of the total planned randomized sample of 1,600. The study team will prepare all documents and reports in such a manner as to allow complete understanding of the study and the results, and will provide the DSMB with the materials in advance of their meeting date, which will scheduled by the DSMB at their convenience. As appropriate, the DSMB may consider recommending for protocol modifications or revisions to the informed consent document if problems with enrollment, accrual, or protocol implementation are identified, or if identified safety events are noted to occur at a rate beyond that which would be expected to occur in the course of standard care based on available research and clinical experience.

Study enrollment and follow up visits will continue during the period of DSMB review and will proceed until study completion unless the sponsor or the PI determines stopping the study is necessary prior to the conclusion of the study.

9 Study Administration, Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial as appropriate and applicable to the study.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. Data will be collected using CRFs developed specifically for the REGAIN trial as well as standardized instruments. Forms will be made available for completion on paper as well as directly into the electronic data management system. Data will be collected from in-person and telephone interviews with study participants and their proxy, and from clinical information contained in medical records. When possible during the follow-up phase of telephone interviewing, data collected by the CCC will be entered directly into the electronic data management system. Hard copy CRFs will be available in case of DMS inaccessibility.

9.4 Data Collection and Management

Data Collection Procedures. All data collection procedures for the REGAIN Trial are outlined above in **Section 6** ("Study Procedures")

Data management procedures. The Data Coordinating Center (DCC) at the University of Pennsylvania will develop a data management system for the collection, validation, storage and management of trial data. The data management system will use a combination of tools to perform the following study functions:

- Subject tracking – to monitor screening and enrollment and produce subject visit schedules
- Eligibility determination and randomization - to evaluate screening data to determine eligibility and randomize subjects according to the randomization schema provided by the Biostatistician
- Comprehensive data collection modules to accommodate all types of trial data

Data management system. All research data for this trial will be stored in an electronic database that is managed by the Clinical Research Computing Unit (CRCU) of the University of Pennsylvania Center for

Clinical Epidemiology and Biostatistics (CCEB). The database will be hosted on secure computing servers and will be restricted to only those individuals who are authorized to work on the trial. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies.

The DMS will exist within an appropriate database structure to support the requirements of the DMS and to promote data security and integrity. Electronic audit trails of changes to database contents will be incorporated into the design and will capture and record those changes automatically. In addition to the trial database where actual results will be maintained, a development database will be created. The development database is a working environment that facilitates the development, testing, troubleshooting, enhancement, and training for the DMS without adversely affecting the integrity of the collected project data.

CRCU servers exist within highly secure computing environments of the CCEB that are the responsibility of the Penn Medicine Academic Computing Services group. This group focuses on providing hardware and software services, systems administration, business continuity, and security services to research projects within the CCEB and other departments in Penn Medicine.

Data Security Measures: The research computing environment has a security component required due to HIPAA; federal, state, and research compliance regulations; and CCEB best practices for safeguarding research data. The CCEB secures its logical network using virtual private network (VPN) protocols and network address translation (NAT) protocols layered on top of the single logical virtual local area network (VLAN). The VPN protocols provide encrypted “data in motion” protections and “fire-walled” connections between each of the physical network segments of the logical network. Applying VPN/VLAN encrypted connections allow all internal CCEB data to “tunnel through” and traverse the University’s physical networks as needed, while maintaining security at the logical CCEB network level, thus ensuring the privacy of the CCEB data and the availability of the data to only CCEB managed resources and users.

In addition to the VLAN and VPN technologies, the CCEB network utilizes the NAT protocols to provide private network addressing within the logical CCEB network. This additional precaution ensures that all network protocols running into or out of the logical CCEB network are essentially “proxy” connections that are only passed through one of several CCEB firewall devices. Providing a proxy service allows the CCEB to monitor, log and control all data and network protocols coming into and going out of its logical network.

The physical building environment for supporting the computing environments required by the CRCU is co-located within a formal data center facility that is managed by University of Pennsylvania; Penn Medicine and Information Systems and Computing personnel. The data center also has uninterrupted power supply (UPS)/diesel subsystems to ensure that adequate and constant electrical power requirements are met at all times, even during prolonged power outages. The data center has secured and limited physical access and is constructed with walls and doors to prevent break-through efforts and/or illegal entry.

Data entry. The CRCU will configure a remote data capture (RDC) module to allow remote data entry from the participating trial sites. The RDC module will be available to any computer with a persistent internet connection and will be run using standard web browser software. The data entry screens will look like the data collection forms as closely as possible to allow visual referencing during data entry, enhancing accuracy and efficiency. Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and skip pattern enforcement. This data entry module will be configured for single data entry.

NDI data will be transmitted from the US CDC's National Center for Health Statistics to CRCU staff or to the DCC or CCC PI via password-protected encrypted CD-ROM or similar media by overnight mail, and will be loaded directly onto the DMS. Following data transfer, the original NDI disk will be stored in a locked safe or secure locked cabinet within the CRCU.

Data Quality Module: The CRCU will configure a module to assess data entered in to the database in relation to a set of rules that describe expectations for those data items. This set of data validation rules will be defined by CRCU clinical data management personnel and the study PI and Biostatistician to identify data items that may have been collected incorrectly or entered into the database inaccurately. The module will run automatically to inspect all newly entered or modified data. Clinical site personnel will review the results of the data validation and take any required corrective action for invalid data. Queries will be recorded and tracked in the data quality module. Corrections identified for individual data items will be managed by the clinical sites. All changes made will be recorded in an electronic audit trail and documented using change control procedures.

The DCC and CCC teams will establish specific training and certification procedures to ensure that all study personnel are well trained in the performance of study procedures, data collection and data entry processes

A Manual of Procedures (MOP) will provide detailed instruction for the performance of screening, enrollment, randomization and follow-up procedures. The MOP will provide instruction in case report form completion, and use of the electronic data management system,

Reports Module: The CRCU will develop a set of standard reports to clearly illustrate the results of trial recruitment efforts and study events, and to document any safety concerns that have occurred during the study. Additional reports may be developed where regular feedback is desirable. Such additional reports may include data entry timeliness and data quality assessments.

9.5 Management of audio recordings of 60, 180, and 365 day interviews:

All post-discharge telephone interviews will be audio-recorded with permission for quality assurance; audio files will be kept in digital format on removable media (e.g. Flash Drive, DVD-ROM) that will be stored in secure, locked cabinets within offices controlled by the PI when not in use. Audio files will be accessed for random auditing of interviews and additionally as needed for quality control by the study PI and CCC staff using PCs located within offices controlled by the PI.

9.6 Records retention

All investigators will retain study essential documents for at least 7 years after the last subject completes the study, or longer if recommended by the IRB, the DSMB or another oversight organization within or outside the University of Pennsylvania.

9.7 Public access plan

A complete, cleaned, de-identified copy of the final dataset used in conducting the final analyses will be made available within one year after completion of the study. The CRCU will remove any patient, site, or other sensitive information from the final database to make it suitable for scientific use. This includes removal of all Personal Health Information (PHI) and indirect identifiers that are not listed as PHI but could lead to "deductive disclosure" such as comment fields and site numbers. Study specific de-identification methods will be documented in the final protocol. Documentation regarding the data and relevant study details will be provided. This includes the annotated case report form (CRF); a text file outlining the structure, variables and contents of each dataset. The study documentation for this trial will include the final protocol, study procedures, data collection forms, descriptions of all variable recoding performed, and a list and links to all primary publications. Datasets and accompanying files will be available on request from the PI or DCC; key datasets will be archived as appropriate to ensure their long-term value and usability.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according a formal monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities, and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The PI will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

11.1 Risks

(1) Risk of Randomization. As treatments will be assigned randomly, the process of randomization will necessarily carry the associated risks and benefits of the specific type of anesthesia to be used here. Both anesthetic regimens to be used in this study are standard of care, with risks and benefits described below;

(2) Anesthesia Regimens. Risks for participation in this study do not go beyond those risks typically associated with spinal or general anesthesia as used in routine care. Medications typically used for general and regional anesthesia (spinal block) are FDA approved to be used alone and in combination for anesthesia. Beyond the study consent, patients will also undergo standard procedural consent to discuss the risks and benefits of regional and general anesthesia as per the routine of the local hospital. Risks associated with spinal anesthesia: Occasionally, regional anesthesia does not provide sufficient pain relief. In these situations, he/she may receive general anesthesia or intravenous pain-relieving drugs to supplement regional anesthesia. The risks of regional anesthesia include, but are not limited to, low blood pressure, itching or allergic reactions to drugs, obstruction or cessation of breathing, headache, and very rarely temporary paralysis, nerve injury, infection or meningitis. Risks of general anesthesia include, but are not limited to, nausea and vomiting, awareness under anesthesia, damage to lips or teeth, sore throat, headache, eye injury or blindness, infection, transfusion reactions (including excessive bleeding and kidney damage), drug reactions (including rash, shock, and cardiac/respiratory arrest), blood clots, lung infections, loss of sensation or limb function, paralysis, stroke, or brain injury, heart failure or heart attack, and death. Patients will have been screened by both their surgical and anesthesia team for allergies to any medications including those commonly used for anesthesia and post operative pain control;

(3) Confidentiality breaches. Risks of breaches of confidentiality are small but nonetheless possible. However, all possible efforts have been taken to ensure the security of study data and minimize the risks of accidental disclosure of identifiable data elements, as outlined below.

11.2 Benefits

At present, insufficient evidence exists to characterize the comparative effectiveness of spinal versus general anesthesia for hip fracture surgery among older adults; if a relative difference in comparative effectiveness between these two modalities of anesthesia is found in the present study, the potential exists that direct benefits of participation could accrue to those patients randomized to a given study arm who may have otherwise received a different type of anesthesia. However, research participants may also receive no direct benefits from participation in this study. For individuals other than the study participants, the present study has substantial potential to yield benefits to individuals with hip fractures. As stated above, gaps in knowledge regarding the comparative effectiveness of regional versus general anesthesia for improving patient-centered outcomes after hip fracture currently limits efforts to improve quality in hip fracture care and has been identified as a key area for hip fracture research by a range of stakeholder groups. Our study will address these gaps in knowledge through the first adequately-powered prospective study to compare the impact of spinal vs general anesthesia for hip fracture surgery on patient-centered outcomes. Given the use of established and conventional anesthesia treatments in both arms of the study, and the potential for this study to benefit a large number of patients with hip fracture, we judge the risks to study subjects to be reasonable in relation to the anticipated benefits to research participants and others.

11.3 Risk/Benefit Comparison.

Based on the considerations listed above, the study could be considered greater than minimal risk to patients. However, the knowledge that may be gained from the present study may impact the care of over 300,000 individuals in the US each year and 1.6 million worldwide. Hip fracture represents a critical public health concern for older individuals and their families; identification of evidence-based treatments that may improve functional and survival outcomes after hip fracture is critical for improving the quality of hip fracture care and reducing the massive burden of death and disability attributable to hip fracture. Moreover, decreasing the burden of disability associated with hip fractures may have positive effects on health care resource use among hip fracture patients. By comparing the effectiveness of two widely used approaches to anesthesia care for hip fracture surgery, the present study has the potential to yield a transformative impact on how hip fracture care is delivered in the US and other countries. Given these considerations, the risks to the study subjects, which will be fully disclosed, and managed and mitigated to the maximum extent possible through appropriate study procedures and supervision, are reasonable in relation to the importance of the knowledge that may result from this study.

11.4 Informed Consent Process / HIPAA Authorization

The site PI, the site Clinical Research Coordinator, or another member of the orthopedic or anesthesia team will obtain informed consent and HIPAA Authorization prior to randomization. The patient will learn about the purpose of the study, the study anesthesia regimens, and data collection procedures and timing at the time of informed consent. For consenting patients, a note will be written in the chart to indicate completion of consent.

Some patients may be too sick or not competent to give permission to enter the study. In these cases, we will attempt to recruit the patient by seeking permission of the family or caregiver who is signing informed consent for the surgical procedure. We believe it is appropriate and ethical to recruit these patients into the trial because these patients are commonly treated with both general and spinal anesthesia in practice. Extrapolation of the results from a study excluding seriously ill or cognitively impaired patients may be unreliable so it is important that direct evidence be obtained by including such patients in the study. For subjects for whom proxy consent is initially obtained, but the patient regains the ability to control medical decisions for themselves by postoperative day 3 or the day of hospital discharge (whichever comes first), direct written consent will be obtained. For subjects who decline participation at this point, no further data will be collected; data collected prior to this point will be retained as per the data management and analysis plan outlined above.

For otherwise eligible patients who decline participation, reasons for refusal will be documented and a limited chart review will be performed with separate consent.

12 Study Finances

12.1 Funding Source

This study is funded through a contract with the Patient Centered Outcomes Research Institute (Washington, DC)

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the applicable University conflict of interest policy(ies).

12.3 Subject Stipends or Payments

No stipends or payments will be provided to study subjects.

13 Publication Plan

The results of this study in whole or in part will be prepared and submitted for publication to professional meetings and/or journals in order to disseminate the information gleaned from this investigation. Subject data will be published in aggregate and will be deidentified prior to analysis in order to protect the confidentiality of study participants.

The publication of study reports will be governed by the REGAIN Publication Policy, which will be developed by a committee to include the PI and selected other investigators. Policies on authorship will be determined by committee vote, and will be consistent with available standards and norms regarding authorship on scientific publications for multicenter randomized trials.

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Perelman School of Medicine
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A RANDOMIZED CONTROLLED TRIAL OF REGIONAL VERSUS GENERAL ANESTHESIA FOR PROMOTING INDEPENDENCE AFTER HIP FRACTURE (REGAIN TRIAL)

A multicenter randomized controlled trial to compare survival, functional recovery, and cognitive outcomes, and postoperative adverse events among patients aged 50 and older receiving spinal versus general anesthesia for hip fracture surgery.

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Funding sponsor	Patient Centered Outcomes Research Institute 828 L St., NW, Suite 900 Washington, DC 20036 Phone: (202) 827-7700 Fax: (202) 355-9558
Grant Number	PCS 1406-18876
Interventions	Standard care spinal anesthesia Standard care general anesthesia
ClinicalTrials.gov Number	NCT02507505

Initial version: A2.2 **-** August 22, 2015
Amended version: A2.3 – March 29, 2016

OCR
Office of Clinical Research

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List of Abbreviations

3D-CAM: 3-minute Diagnostic Assessment for CAM-Defined Delirium

AE: Adverse Event

BPI: Brief Pain Inventory

CCC: Clinical Coordinating Center

CRC: Clinical Research Coordinator

DCC: Data Coordinating Center

DSMB: Data Safety Monitoring Board

IRB: Institutional Review Board

NSQIP: National Surgical Quality Improvement Program

OAAS: Observer's Assessment of Alertness/Sedation Scale

PI: Principal Investigator

REGAIN: Regional versus General Anesthesia for promoting Independence after Hip Fracture

SBT: Short Blessed Test of cognition

WHODAS 2.0: WHO Disability Assessment Schedule 2.0

Investigator Approval Statement

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with the University of Pennsylvania Clinical Coordinating Center and Data Coordinating Center during the study. I will adhere to the Declaration of Helsinki and its amendments, the International Conference on Harmonization (ICH) principles of Good Clinical Practice (GCP; including archiving of essential study documents) and all applicable regulations and guidelines of the country in which the study is conducted.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

REGAIN

A Randomized Controlled Trial of Regional versus General Anesthesia for Promoting Independence after Hip Fracture

Final Protocol Revised: March 29, 2016

Study Summary

Title	**A Randomized Controlled Trial of Regional versus General Anesthesia to Promote Independence after Hip Fracture (REGAIN Trial)**
Short Title	REGAIN Trial
Methodology	Randomized, active-controlled trial
Study Duration	6 years
Single or multicenter design	Multicenter
Objectives	**1.** To test the effect of spinal versus general anesthesia on recovery of walking at 60 days after randomization. **2.** To measure the impact of spinal versus general anesthesia on overall health and disability, return to the pre-fracture place of residence, pain, and mortality, and cognition at approximately 60, 180 and 365 days after randomization **3.** To assess the tolerability of spinal versus general anesthesia for hip fracture surgery, and the association of spinal versus general anesthesia with inpatient mortality and major morbidity, including postoperative delirium.
Number of Subjects	Total enrollment (consented patients): 2,424; Total randomized sample: 1,600
Main Inclusion and Exclusion Criteria	**Inclusion criteria:** Hip fracture requiring surgical treatment; age ≥ 50 years; ability to walk without human assistance before fracture **Exclusion criteria:** Concurrent surgery not amenable to spinal anesthesia; absolute contraindications to spinal anesthesia; patients known or suspected to be at elevated risk for malignant hyperthermia; periprosthetic fracture; and by determination of the surgeon, the treating anesthesiologist, or the site Clinical Director or their designate.
Interventions	Standard care spinal anesthesia Standard care general anesthesia
Statistical Methodology	Data will be analyzed via intent-to-treat (primary) and per-protocol methods; binary outcomes will be analyzed using standard two-sample hypothesis tests and multivariate regression models accounting for necessary stratification factors.
Safety Evaluations	Safety evaluations will occur via medical record review on postoperative day 1-3 and at discharge for selected serious adverse events.
Data and Safety Monitoring Plan	The PI and the DSMB will be responsible for monitoring the data quality and the ongoing safety of subjects.

BACKGROUND AND STUDY RATIONALE

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (GCP) (International Conference on Harmonization ICHE6), the Code of Federal Regulations Title 21, and other applicable government regulations and Institutional research policies and procedures. All episodes of noncompliance will be documented.

The purpose of this active comparator study is to evaluate the effect of two different standard care approaches to anesthesia care for hip fracture surgery on recovery of ambulation at approximately 60 days (primary outcome) and other patient-centered outcomes measured at 365 days (plus or minus 60 days). The two approaches are spinal anesthesia (spinal block) and general anesthesia. Our overarching hypothesis is that patients undergoing hip fracture surgery with spinal anesthesia will demonstrate improved ambulation at approximately 60 days and better outcomes across a range of patient-centered endpoints compared to patients receiving general anesthesia.

1.1 Background and Relevant Literature

Hip fracture is a clinical condition that involves a break in the femur (hip bone) near where it attaches to the pelvis (Figure 1). Over 90% of hip fractures occur in individuals aged 50 or older, most commonly resulting from low-energy traumatic injuries, such as falls from standing in the context of established osteoporosis, chronic illness, or disability. Surgical treatment, via fixation of the fractured bone or partial or total replacement of the hip joint, is indicated for all types of hip fractures and approximately 95% of hip fracture patients undergo surgery.

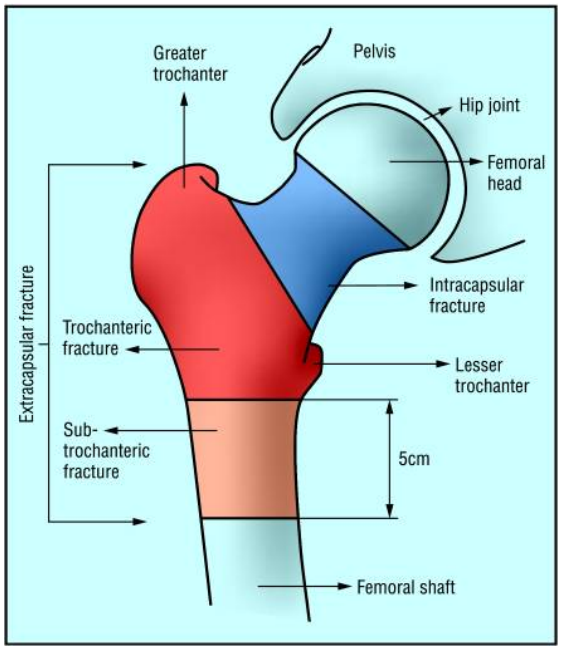

Figure 1: Locations of common hip fractures[1]

Hip fractures occur more than 300,000 times each year in the US and over 1.6 million times each year worldwide. Hip fractures carry major consequences for the individual and society.[6, 7] Within 12 months of fracture, 25% of patients die,[8, 9] and half of previously community-dwelling patients either die or require nursing home admission.[10] Among patients who survive to 12 months, 40% of those who could walk independently before fracture require human assistance to walk 10 feet.[11] Hip fractures create substantial needs for informal caregiving [12, 13] and post-acute and long-term care that carry major costs to society;[14] the estimated costs attributable to hip fractures in the US exceeded $12 Billion in 2005 and will exceed $18 Billion by 2025.[15] Moreover, the disability caused by hip fractures matters to older adults. In a study of patient views on hip fracture, 194 women aged 75 or older read hypothetical scenarios describing a "good" hip fracture after which they would continue to live independently, and a "bad" hip fracture that would require admission to a nursing home. *Of women surveyed, 80% stated that they would rather die than experience the loss of independence associated with a "bad" hip fracture.*[16]

No evidence-based interventions now exist to improve functional outcomes after hip fracture surgery beyond the immediate postoperative period.[17, 18] Nearly all hip fracture patients require orthopedic surgery and anesthesia,[19-21] making the anesthetic care episode a major opportunity to impact outcomes.[22]

Spinal and general anesthesia (defined below) represent the two standard care approaches to anesthesia for hip fracture surgery.[23] Basic and clinical research has identified multiple plausible mechanisms by which spinal anesthesia may improve outcomes after hip fracture; nonetheless, major guidelines and systematic reviews have identified key evidence gaps [24-28] and anesthesia care for hip fracture varies markedly in practice.[29] While spinal and general anesthesia for hip fracture have been previously compared in retrospective studies and small randomized trials, much of the available prospective trial data is old and may not be reflective of current clinical practice.

REGAIN will be the first pragmatic multicenter prospective randomized trial of spinal versus general anesthesia for hip fracture surgery designed to evaluate the association of anesthesia technique with functional recovery after hip fracture. As such, it will fill critical evidence gaps to inform policy and practice.

1.2 Name and Description of the Interventions

We will compare two widely used approaches to anesthesia for hip fracture surgery.

General anesthesia uses injected or inhaled medications to keep people unconscious during surgery. Since general anesthesia depresses breathing and impairs protective airway reflexes, invasive airway interventions such as breathing tube placement and mechanical ventilation are usually required.[30]

Spinal anesthesia uses local anesthetic medications injected into the fluid surrounding the spinal cord to temporarily numb the legs and lower abdomen. Spinal anesthesia is the most widely used type of regional anesthesia for hip fracture surgery.[31, 32] While intravenous sedation is typically used for comfort with spinal anesthesia, invasive airway interventions are not typically required.[33]

1.2.1 Clinical Data to Date

Multiple clinical and laboratory studies provide evidence for physiologic effects of general and regional anesthesia that may plausibly lead to differences in important downstream patient-centered outcomes. These effects are summarized in **Figure 2.**

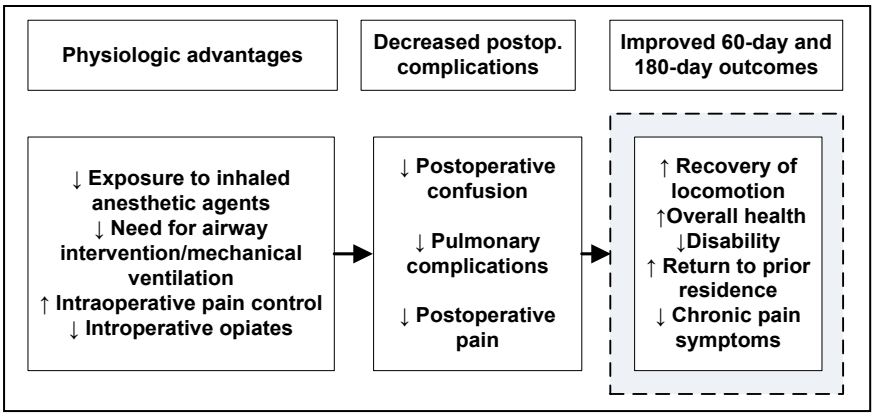

Figure 2: Proposed causal pathway linking spinal versus general anesthesia to improved patient-centered end-outcomes after hip fracture.

Pulmonary effects of general versus spinal anesthesia: General anesthesia negatively impacts lung function by impairing natural processes that prevent buildup of excess mucous,[34-36] keep individual lung units (alveoli) open,[37, 38] and maintain a normal breathing rate.[39-41] General anesthesia also impairs the function and coordination of muscles involved in breathing.[42, 43] In contrast, spinal anesthesia has minimal effects on lung function.[44-46] Compared to general anesthesia, spinal anesthesia is associated with higher blood oxygen levels after hip fracture surgery[47-49] and lower rates of postoperative pneumonia.[48, 50, 51] A recent large retrospective study by the PI found a lower odds of pulmonary complications with regional anesthesia among 18,159 patients undergoing hip fracture surgery (adjusted odds ratio (OR) 0.75, 95%CI 0.64 to 0.89).[52]

Effects on pain pathways: With general anesthesia, intravenous opiates like morphine are commonly used to treat pain; under-dosing of these drugs and inadequate pain control may lead to the development of long-term pain by sensitizing neurons that transmit pain signals to the brain ("central sensitization").[53-55]

Spinal anesthesia prevents central sensitization by blocking transmission of pain signals at the level of the spinal cord, potentially contributing to better short- and long-term pain outcomes.[56-58]

Effects on cognition: General anesthesia impairs brain cell (neuron) function by influencing neuron gene transcription;[59, 60] signaling of impulses between neurons;[61-64] and systems that balance levels of important ions, such as calcium, within neurons.[65] General anesthesia has been shown to impair short- and long-term memory acquisition.[66-69] A 2004 meta-analysis of seven trials[47, 48, 50, 51, 70-72] found lower rates of postoperative confusion among patients who received spinal versus general anesthesia for hip fracture surgery (relative risk (RR), spinal versus general anesthesia: 0.50, 95% confidence interval (CI): 0.26 to 0.95).[26] Additionally, a large retrospective study suggested lower rates of cognitive impairment with spinal anesthesia at 6 and 12 months after hip fracture.[73]

Effects on patient-centered end-outcomes: Few prospective studies to date have examined differences in patient-centered end-outcomes with spinal versus general anesthesia for hip fracture surgery.

Mortality: A 2004 meta-analysis of eight small randomized trials of spinal versus general anesthesia for hip fracture observed a lower 30-day mortality with spinal anesthesia (RR 0.69, 95% CI: 0.50, 0.95).[26] Nonetheless, the randomized trials included in this meta-analysis have substantial limitations; many were completed prior to the 1990's, and may thus have limited relevance to current practice and the methodological quality of included trials was judged to be low overall.[25, 26] More recently, in a retrospective study of 18,159 hip fracture patients, the PI (Neuman) observed significant decreases in the adjusted odds of in-hospital mortality with spinal versus general anesthesia (OR: 0.71, 95% CI 0.54, 0.93),[52] although subsequent non-randomized analyses have yielded equivocal results regarding the association of anesthesia type with in-hospital[74] or 30-day mortality[29] differences. Importantly, even well-done non-randomized studies of anesthesia care for hip fracture patients are substantially limited by potential selection bias: since patients who receive regional anesthesia tend to be older and sicker than those who receive general anesthesia,[29, 52, 75] non-randomized studies will tend to underestimate any true benefits of spinal anesthesia.

Functional endpoints: To date, the association between anesthesia technique and functional endpoints has only been investigated in non-randomized studies. Historical cohort studies have shown inconsistent associations between anesthesia technique and locomotion after hip fracture.[76,73] As a pilot investigation for REGAIN, we conducted a retrospective (non-randomized) analysis of data collected in the FOCUS trial,[77, 78] a 47-center trial of transfusion management strategies in 2,016 hip fracture patients. While we found that patients who received spinal anesthesia were older than those who received general anesthesia (mean age 82.5 years vs. 80.9 years, P<0.001) they were slightly more likely to be alive and able to walk independently at 60 days (65.3% vs 64.9%) although this difference was not statistically significant (p=0.86).

Evidence gaps: Major gaps in evidence persist regarding the comparative effectiveness of common anesthesia options for hip fracture surgery. A 2011 systematic review by the UK Clinical Guideline Centre concluded that "no recent randomized trials were identified that fully address" the clinical effectiveness of regional versus general anesthesia for hip fracture surgery, and found that the available evidence "is old and does not reflect current practice."[25] The 2014 American Academy of Orthopedic Surgeons' guidelines for hip fracture care also note that available randomized studies are likely to be outdated and that "future research involving appropriately randomized patients may yet delineate which anesthesia technique is more appropriate in this patient population."[24]

2 Study Objectives

The purpose of the REGAIN trial is to evaluate the effect of two different standard care approaches to anesthesia for hip fracture surgery (spinal and general anesthesia) on recovery of ambulation at approximately 60 days (primary outcome) and other patient-centered outcomes measured at up to approximately 14 months (365 days plus or minus 60 days) after randomization. The overarching hypothesis of this study is that patients who receive spinal anesthesia will demonstrate improved

ambulation at approximately 60 days and have better outcomes across a range of patient-centered endpoints compared to patients who receive general anesthesia.

2.1 Primary Objective

- To test the effect of spinal versus general anesthesia on recovery of ambulation at approximately 60 days after randomization.

2.2 Secondary Objectives

- To measure the impact of spinal versus general anesthesia on overall health and disability, cognition, return to the pre-fracture place of residence, pain, and mortality at approximately 60, 180, and 365 days after randomization.
- To assess the association of spinal versus general anesthesia for hip fracture surgery with in-hospital mortality, delirium, medical complications, and pain.
- To assess the association of spinal versus general anesthesia for hip fracture surgery with satisfaction with care.

3 Study Population and Duration of Participation

3.1 Inclusion Criteria

● Clinically or radiographically diagnosed intracapsular or extracapsular hip fracture
● Planned surgical treatment via hemiarthroplasty, total hip arthroplasty or appropriate fixation procedure
● Age ≥ 50 years
● Ability to walk 10 feet or across a room without human assistance before fracture

3.2 Exclusion Criteria

● Planned concurrent surgery not amenable to spinal anesthesia.
● Absolute contraindications to spinal anesthesia, including: (1) Known or suspected congenital or acquired coagulopathy; (2) active use of pharmacologic anticoagulants within a timeframe defined to contraindicate neuraxial block placement by available American Society of Regional Anesthesia guidelines;[79] (2) known or suspected unrepaired critical or severe aortic stenosis; (3) known or suspected active skin infection at the planned needle insertion site; (4) known or suspected elevated intracranial pressure contraindicating dural puncture.
● Patient is known or suspected to be at elevated risk for malignant hyperthermia
● Periprosthetic fracture
● Prior participation in the REGAIN trial
● Prisoner status
● Determination by the attending surgeon, the attending anesthesiologist, or the site Clinical Director or their designate, that the patient would not be suitable for randomization.

3.3 Subject Recruitment

Hip fracture is an acute condition requiring urgent hospitalization; as such, all subjects will be recruited in hospital settings between the time of presentation and the time of surgery. Orthopedic surgeons performing hip fracture surgery at each recruiting site will be contacted in advance of the initiation of study accrual to assess willingness to allow for patients to be enrolled. Patients under the care of non-participating orthopedic surgeons will not be recruited into this study. A list of non-participating orthopedic surgeons will be maintained by each site Clinical Director.

Site CRCs, Clinical Directors and other appropriate personnel will use multiple strategies to identify potentially eligible patients, potentially including interval calls to the hospital admissions office, specific hospital floors or units, relevant attendings, residents, or physician extenders (physician assistants or advanced practice nurses); reviews of inpatient census lists and operating room schedules; and requests to physicians and physician extenders, emergency room personnel, ward clerks and floor nurses to contact site study staff when a hip fracture patient is admitted to the hospital.

For potentially eligible patients, the site CRC, site Clinical Director or other appropriately trained study staff member will approach the patient and/or their proxy between the time of diagnosis and the time of surgery to explain the study, complete a brief screening evaluation, and obtain informed consent. Alternately, members of the healthcare team may initially query patients or their proxies regarding potential interest in participation in the REGAIN trial; for interested patients or their proxies, the study team will be contacted to initiate recruitment and enrollment.

3.4 *Duration of Study Participation*

The planned maximum duration of study participation will be approximately 14 months from the date of randomization (i.e. 365 days plus or minus 60 days). Additional data on survival beyond this point may be obtained from administrative sources (e.g. NDI) where available.

3.5 Total Number of Subjects and Sites

Recruitment will end when approximately 2,424 subjects are enrolled. It is expected that this approximate number of subjects will be enrolled (i.e. informed consent for participation will be obtained) in order to produce approximately 1,600 randomized patients. This estimate is based on an assumption that one in three patients (33%) who undergo consent prior to surgery will be found to be ineligible for randomization on the day of surgery due to active clinical issues, timing of medication dosing, or clinical assessments by treating physicians or the site Clinical Director or their designate.

3.6 *Enrollment of children, pregnant women, fetuses, neonates, or prisoners:*

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

4 Investigational Plan

4.1 General Design

Randomized, multicenter, active comparator study of two alternative standard care approaches to anesthesia for hip fracture. Study endpoints will be assessed via in-person interview (during hospitalization), medical record review, telephone interview (after hospital discharge), and a vital records database search.

4.1.1 Screening Phase

Subjects will be screened in person by site CRCs, the site Clinical Director, or other designated study staff between the time of presentation and the time of surgery. Written informed consent and HIPAA authorization will be obtained in person from patients or their proxies (in cases where patients are unable to provide informed consent) by site CRCs, the site Clinical Director, or other designated study staff. A series of questions will be asked of patients or their proxies to determine if the potential subject is within the correct age range and to assess other inclusion and exclusion criteria. For potential subjects who may be eligible based on these criteria, written informed consent will be obtained from patients or (where necessary) their proxies.

Consenting patients will undergo an interview, to be carried out by site CRCs, the site Clinical Director, or other designated study staff, to collect necessary pre-randomization baseline data. Potentially eligible patients will undergo a final pre-randomization screening evaluation on the day of surgery to verify eligibility for randomization; since the assigned anesthesiologist is often not known before the day of surgery, and since changes in patient clinical status over time may impact eligibility, this evaluation will be

required to occur on the day of surgery. Patients deemed eligible for study inclusion at this point will proceed to the study intervention phase.

4.1.2 Study Intervention Phase

For randomized patients, the intervention phase will comprise the period in which they are undergoing anesthesia care for hip fracture surgery. Prior to the start of anesthesia care, the treating anesthesiologist will be notified by the site Clinical Director, CRC, or other designated personnel, regarding the randomization status of the patient. As described below, patients will be randomized to one of two pragmatic treatment protocols that will instruct the treating anesthesiologist to deliver a standard care general anesthetic or a standard care spinal anesthetic. The study intervention phase will comprise the intraoperative anesthesia care episode, with the choice of primary anesthetic modality determined by this randomization assignment.

4.1.3 *Follow Up Phase*

The follow up phase will extend from the end of the anesthesia care episode to up to approximately 14 months (i.e. 365 days +/- 60 days) after the date of randomization.

4.1.4 Allocation to Interventional Group

Participants will be randomly assigned to one of the two treatment regimens in a 1:1 ratio. Randomization will occur on the day of surgery via an automated algorithm constructed by the study Biostatistician. For each arm, balanced randomization of subjects, stratified by site, gender, and fracture type (intracapsular versus extracapsular), will be achieved by permuted block randomization with a variable block size.[80, 81] The randomization seed and actual algorithm will be kept by the study Biostatistician. Study procedures for randomization of subjects are detailed in Section 6.2.1 below.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Independence in walking at 60 days after randomization (Primary outcome). The primary outcome will be assessed by patient and/or proxy telephone interview at 60 days after randomization (+/- 30 days). Patients who report being unable to walk 10 feet or across a room without human assistance, or who die within 60 days of fracture will be classified as treatment failures; patients who require a cane or walker, but not human assistance, will not be classified as treatment failures, although data regarding the need for assistive devices will be collected for analysis as a secondary outcome. This outcome will also be assessed by telephone interview at 180 days (+/- 45 days) and at 365 days (+/- 60 days) where feasible for analysis as secondary study endpoints.

4.2.2 Secondary Study Endpoints

Overall health and disability. Overall health and disability will be assessed by in-person patient and/or proxy interview at baseline and by telephone interview at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization via the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0).[82] The WHODAS 2.0 is a patient-reported outcome that assesses cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society. It can be administered in person or by telephone in around 5 minutes.[83] The WHODAS 2.0 is scored on a scale from 0 (no disability) to 4 (extreme disability) for each of 12 items; item scores are summed to obtain a total score ranging from 0-48. The total score is divided by 48 and multiplied by 100 to convert it to a percentage of the maximum disability score; disability is classified as none (0-4%), mild (5-24%), moderate (25-49%), severe (50-95%) and complete (96-100%).[83, 84] The WHODAS has been validated across multiple conditions,[85-90] and has good criterion and convergent validity for assessing postoperative recovery at 3, and 6 months, with excellent responsiveness and internal consistency (Chronbach's Alpha > 0.90).[91]

Need for assistive devices for walking. The need for assistive devices for walking (e.g. cane, walker) will be assessed by in-person patient and/or proxy interview at baseline and by telephone interview at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization.

Ability to return home. All patients will be queried by telephone interview regarding location of residence at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization. For patients not residing in long-term nursing homes prior to fracture (93% of all U.S. hip fracture patients),[92] the percentage returning home at each time point will be assessed as a secondary outcome.

Chronic pain. Pain symptoms will be assessed by patient and/or proxy telephone interview at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization using the Numeric Rating Scale (NRS), by which pain symptoms are rated from 0 (no pain) to 10 (worst pain imaginable); pain items will assess the extent of pain at worst and on average over the past 24 hours, using similar wording to selected Brief Pain Inventory items.[93, 94]An additional item will query patients as to whether they are actively taking prescription medications for pain.

All-cause mortality. Vital status will be assessed via patient and/or proxy telephone interview at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization. Additionally, a National Death Index search will be performed in the final year of the study for all patients enrolled up to that point; studies evaluating NDI accuracy in determining mortality have reported rates of 83%-98%.[95, 96]

Cause of death. Cause of death will be determined via National Death Index search in the final year of the study for all patients enrolled up to that point.

Acute postoperative pain. Pain during hospitalization will be assessed by site CRCs or other appropriate staff via in-person patient and/or proxy interview before surgery and daily up to postoperative day 3 or the day of discharge (whichever occurs first) using a 0-10 Numeric Rating Scale; pain items will assess the extent of pain at worst and on average over the past 24 hours, using similar wording to selected Brief Pain Inventory items.[93, 94].

Satisfaction with care. Satisfaction with anesthesia care will be assessed by site CRCs or other appropriate staff via in-person interview on postoperative day 3 or the day of discharge (whichever occurs first) via the Bauer Patient Satisfaction Questionnaire,[97] as well as additional items assessing to undergo or recommend a similar anesthetic in the future.

Cognitive function. Cognitive function will be assessed via in-person interview at baseline, and via telephone interview via the Short Blessed Test (SBT), a well-validated brief cognitive screen appropriate for telephone administration at 60 days (+/- 30 days), 180 days (+/- 45 days), and 365 days (+/- 60 days) after randomization.[4, 98] The SBT is summarized in Table 1.

Postoperative delirium. We will assess patients for the presence of delirium via the 3D-CAM assessment tool via in-person interview at baseline and daily up to postoperative day 3 or the day of discharge (whichever occurs first). The 3D-CAM is a well-validated brief tool with high sensitivity and specificity for delirium.[99, 100]

Inpatient mortality and major inpatient morbidity. In-hospital mortality and other major intraoperative or postoperative complications will be assessed via chart review by site CRCs or other appropriate staff following hospital discharge, death, or at 30 days after randomization, whichever occurs first. We will assess the occurrence of major postoperative complications including but not limited to: (1) postoperative bleeding requiring transfusion; (2) myocardial infarction; (3) congestive heart failure; (3) stroke or transient ischemic attack; (4) pneumonia; (5) urinary tract infection; (6) wound infection; (7) thromboembolic complications; (8) unplanned intubation; (9) prolonged mechanical ventilation; (10) acute renal failure; (11) cardiac arrest requiring CPR or defibrillation; (12) return to the operating room. Complication definitions for use in REGAIN will adapt standard definitions, such as those used by the National Surgical Quality Improvement Program.[101]

Table 1: Short Blessed Test of orientation, memory, and concentration[4]			
Item	Max. # of errors	Weight	Maximum score (errors x weight)
1. What *year* is it now?	1	4	4
2. What *month* is it now?	1	3	3
Memory phrase: Repeat this phrase after me: John Brown, 42 Market Street, Chicago	N/A	N/A	N/A
3. About what *time* is it? (within 1 hour)	1	3	3
4. *Count* backwards from 20 to 1	2	2	4
5. Say the months of the year in reverse order.	2	2	4
6. Repeat the memory phrase.	5	2	10
Maximum total score			28
To score the SBT, the interviewer records the number of errors on each item up to the maximum number of errors allowed for each item. The number of errors on each item is multiplied by that item's weighting factor to obtain the item score. Item scores are summed to obtain a total score between 0 and 28. Scores of 0-4 indicate normal cognition; scores of 5-9 indicate impairment consistent with early dementia; and scores of 10 or more indicate impairment consistent with dementia.[5]			

4.2.3 Primary Safety Endpoints

Spinal anesthesia and general anesthesia are standard care approaches with longstanding track records of safety in appropriately selected patients. The primary safety evaluation will assess whether the adverse event profile associated with participation in the REGAIN trial differs meaningfully from the adverse event profile that could be expected with spinal and general anesthesia for hip fracture surgery in typical clinical practice. We will collect data on the following known or established potential risks of spinal and/or general anesthesia:

- Intraoperative cardiac arrest requiring CPR caused by anesthetic medications or techniques
- Malignant hyperthermia requiring dantrolene or intraoperative anaphylaxis caused by medications used to induce or maintain general or spinal anesthesia
- Intraoperative aspiration resulting in aspiration pneumonia or aspiration pneumonitis
- Epidural hematoma requiring surgical intervention occurring within 24 hours of spinal anesthesia
- Paralysis of the lower extremities lasting greater than 24 hours following spinal anesthesia
- Fall within 12 hours of anesthesia care
- Unplanned postoperative mechanical ventilation lasting greater than 6 hours in a patient not previously requiring mechanical ventilation

These endpoints will be assessed via medical record review for the first 3 postoperative days and at the time of discharge; for patients discharged prior to postoperative day 3, these endpoints will be assessed through the day of discharge.

5 Study Intervention

5.1 Description

Patients will be randomized to receive standard care spinal anesthesia or standard care general anesthesia. The administration of anesthesia will be carried out in the course of routine care by practicing anesthesiologists, residents, nurse anesthetists and other appropriately trained and credentialed clinical staff at each study site. Prior to study initiation, anesthesia staff will be queried by the site Clinical Director regarding their willingness to participate in the study and non-participating anesthesia staff will be identified by the Clinical Director. Additionally, Clinical Directors will identify anesthesia staff who are eligible to provide care for study cases; experience- or skill-based standards for anesthesiologist participation in the REGAIN trial will be determined locally based on the judgment of the site Clinical Director and other study staff. As anesthesia care for patients enrolled in the REGAIN trial will be delivered by participating anesthesiologists as a part of their routine job function, participating anesthesiologists will not be considered part of the study team unless involved in other aspects of the REGAIN trial. Patients who will be under the care of anesthesia staff at the time of induction of anesthesia who are unwilling to participate in REGAIN or who the site Clinical Director has determined to be ineligible for participation in REGAIN will be excluded from randomization.

The intervention will occur by providing the assigned clinical anesthesia staff instructions directing them to perform a standard care spinal anesthetic or a standard care general anesthetic (below). These regimens use standard terminology and do not require specialized techniques, drugs, or monitors beyond those available and in common use in standard care settings. All participating anesthesia staff will undergo a brief orientation to the protocol by the site Clinical Director; instructions will be provided that all aspects of anesthesia care within the protocol should adhere to national, local, and individual standards of practice for the provision of spinal or general anesthesia, including but not limited to: the location of block administration (OR vs. designated block room); medication selection and dosing; decisions to convert from spinal to general anesthesia; postoperative analgesia; and decisions regarding the appropriate duration and number of attempts permitted to perform a spinal anesthetic or to induce general anesthesia.

5.2 Intervention Regimen

At the time of randomization, providers will receive instructions regarding anesthesia care similar to the statements shown below, allowing for minor wording changes or revisions for clarity.

Provider instructions:

Treatment arm 1 (spinal anesthesia): *Please perform a single-shot spinal anesthetic, with sedation as needed for block placement and intraoperative comfort. Please titrate any intraoperative sedation to maintain arousability to tactile stimulus or voice. Conversion to general anesthesia is permitted if required by clinical circumstances. Please conduct all other aspects of anesthesia care, including monitoring, medication selection and dosing, supplemental nerve blocks, and management of intraoperative events as per your usual routine.*

Table 2: Observer's Assessment of Alertness/Sedation[2, 3]

Score	Subject responsiveness	Sedation level
5	Responds readily to name spoken in normal tone	Alert
4	Lethargic response to name spoken in normal tone	Light sedation
3	Responds only after name is called loudly and/or repeatedly	Moderate sedation
2	Responds only after mild prodding or shaking	Moderate sedation
1	Does not respond to mild prodding or shaking	Deep sedation

For patients randomized to receive spinal anesthesia, treating anesthesiologists will receive instructions to document the level of sedation based on the Observer's Assessment of Alertness/Sedation Scale (OAAS), a simple, validated measure of alertness among sedated subjects.[2, 3] The OAAS scoring system to be used in the REGAIN trial appears in Table 2.

Provider instructions: Treatment arm 2 (general anesthesia): *Please perform a general anesthetic. Please use an inhaled anesthetic agent for maintenance and use intravenous opiates as needed for analgesia. Airway management may be via endotracheal tube, laryngeal mask airway, or other device as dictated by clinical circumstances. Please conduct all other aspects of anesthesia care, including monitoring, medication selection and dosing, supplemental nerve blocks and management of intraoperative events as per your usual routine.*

5.3 Blinding

Due to the nature of the study intervention, it will not be possible to blind patients or treating providers (anesthesiologists or surgeons) to treatment assignment.
As permitted by staff availability and site resources, we will encourage site staff to perform the postoperative day 1-3 3D-CAM assessments in a blinded fashion by having these assessments performed by an individual other than the team member(s) who are responsible for obtaining the randomization assignment (see Section 6.2.1, "Randomization") and conducting chart reviews for adverse safety events. Additionally, where appropriate, patients will be instructed to not inform the 3D-CAM assessor of the type of anesthesia they received. If this is not possible based on staff availability or site resources, we will not require blinded collection of in-hospital outcomes data.

Post-discharge outcomes, including the primary study outcome, will be assessed by centrally by telephone. Telephone follow-up for post-discharge outcomes assessment will be carried out by University of Pennsylvania CCC staff who will be blinded to treatment assignment.

Assessments of aggregate data related to patient characteristics and study outcomes will occur in a blinded fashion such that investigators cannot determine subject randomization assignment; unblinding at the level of the individual patient will be permitted as needed for making determinations of relatedness for adverse events (see section 8.3 below). Unblinding procedures for the overall study are described below in section 8.5 below.

5.4 Subject Compliance Monitoring

The PI and/or CCC staff will assess the type of anesthesia actually received via retrospective chart review, to be completed by site CRCs or other study personnel following death, hospital discharge, or postoperative day 30, whichever comes first. While the type of anesthesia received will be investigated to assess for the extent of crossover between study arms, such crossover will not be considered to represent protocol non-compliance, since treatment regimens permit deviations from assigned treatments based on clinical rationale. Similarly, for patients randomized to spinal anesthesia, sedation beyond arousability to voice or tactile stimulus will not be considered to represent non-compliance, since study protocols allow for provider selection and dosing of sedation based on clinical rationale.

To assess study performance, data on anesthesia care will be reviewed for each recruiting site after the first 10 subjects at each site are randomized. Further site-level analyses as to assess safety events and protocol implementation will be performed on an as-needed basis.

6 Study Procedures

6.1 Screening phase

6.1.1. Initial screening visit

The initial screening visit will be carried out by site CRCs or other appropriate staff between the time of presentation and the time of surgery. It will involve a patient and/or proxy interview and medical record review to assess inclusion and exclusion criteria. Data will be recorded on the Initial Screening Visit Form and entered into the online DMS. Written informed consent will be obtained at this visit and documented in the medical record. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *Informed Consent*
- *HIPAA Authorization*
- *Screening interview (Age; ability to walk 10 feet without assistance prior to fracture; receipt of selected anticoagulant or antiplatelet medications; information on malignant hyperthermia risk; gender, ethnicity, and race)*
- *Medical record review (Planned surgical procedures; history of critical or severe aortic stenosis, elevated intracranial pressure, or lumbar skin infection; available laboratory data on platelets, INR and PTT)*

6.1.2. Baseline data collection visit

The baseline data collection visit will be carried out by site CRCs or other appropriate staff between the time of presentation and the time of surgery. It will involve a patient or proxy interview and medical record review to assess relevant pre-fracture and pre-randomization covariates. Data will be recorded on the Baseline Data Collection Visit Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

Data will also be collected at this visit regarding patient and proxy contact information as needed to facilitate subsequent telephone follow-up; patient social security number and Medicare number as

needed to facilitate data linkages to the NDI and Medicare claims; and names and contact numbers of two additional contacts who do not live with the patient who may be available to facilitate follow-up in the event that we are unable to reach the patient. While information on alternative contact individuals will be collected from patients to assist with follow-up, availability of an alternative contact is not a requirement for participation in the REGAIN trial. Contact data will be stored on the Patient Contact Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use. Forms including patient contact information will be stored separately from all other CRFs.

- *Medical history interview and medical record review (Date of birth; comorbidities; height; weight; do-not-resuscitate status; most recent available heart rate, blood pressure, and oxygen saturation values; fracture location and laterality; supplemental oxygen or mechanical ventilation; most recent available serum creatinine; pre-fracture pain medication use)*
- *Pre-fracture ambulation independence questionnaire*
- *Pre-fracture residential status assessment (i.e. residence at home, in a nursing home, etc…)*
- *Short Blessed Test (cognition)*
- *3D-CAM (delirium)*
- *WHODAS 2.0 (overall health and disability prior to fracture)*
- *Pain symptom questionnaire (average and worst pain over past 24 hours; pain prior to hip fracture)*
- *Brief Resilience Scale (resilience to adversity)*
- *Patient, proxy, and secondary contact information (Patient/proxy telephone numbers, addresses, e-mails; patient social security number and Medicare number; names, telephone numbers, and home addresses of two additional contacts not living with the patient to facilitate follow-up.)*

6.1.3. Day of surgery screening visit

The day of surgery screening visit will be carried out by site CRCs or other appropriate staff on the day of surgery and will involve a medical record review and an interview with treating physicians to assess patient appropriateness for randomization. Patients with identified contraindications to spinal anesthesia will be excluded prior to randomization. Data will be recorded on the Day of Surgery Screening Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *Medical record review (Receipt of selected anticoagulant or antiplatelet medications; available laboratory data on platelets, INR and PTT)*
- *Physician verification of eligibility*

6.2 Study Intervention Phase

6.2.1 Randomization

Randomization will be carried out on the day of surgery; randomization will be performed centrally through the study electronic DMS. The site CRC, Clinical Director or other study staff will obtain the randomization assignment electronically from the DMS and will communicate the treatment assignment to the anesthesia team on the day of surgery verbally in person or by telephone, e-mail, text, or other appropriate modality. Designated alternate study personnel who can access the randomization assignment will be identified by the PI and the site Clinical Director to serve as a backup in the event that the site Clinical Director is not available. In the event that the DMS is not available or cannot be accessed by study personnel, the randomization assignment will be communicated to appropriate site personnel by directly by the PI or designated CCC or DCC staff.

6.2.2 Intraoperative phase

All intraoperative care will be carried out by practicing clinicians at the study site.

- *Standard care spinal anesthesia or standard care general anesthesia*

- *Measurement of sedation level via OAAS scale*
- *Monitoring, clinical management, and additional anesthesia procedures as dictated by standard care*

6.3 Follow Up Phase

6.3.1 Postoperative day 1 and 2 visits

Patients will be visited on the first and second postoperative days by site CRCs or other study personnel to complete an in-person interview to assess delirium and pain. Data will be recorded onto the Postoperative Day 1 and 2 Visit Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *3D-CAM assessment (delirium)*
- *Pain symptom questionnaire (average and worst pain over past 24 hours)*
- *Postoperative mortality assessment*

6.3.2 Postoperative day 3 visit

Patients will be visited on the third postoperative days by site CRCs or other study personnel to complete an in-person interview to assess delirium, pain, and satisfaction with anesthesia. Data will be recorded onto the Postoperative Day 3 Visit Form and entered into the online DMS. For patients discharged on postoperative day 1 or 2, this interview will be completed on the day of discharge in lieu of the postoperative day 1 or 2 interview described above. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *3D-CAM assessment (delirium)*
- *Pain symptom questionnaire (average and worst pain over past 24 hours)*
- *Postoperative mortality assessment*
- *Anesthesia satisfaction questionnaire (satisfaction with anesthesia care)*

6.3.3 Post-discharge medical record review

Site CRCs will complete a detailed chart abstraction to assess intraoperative events and major postoperative adverse events occurring up to the date of discharge, death, or at postoperative day 30, whichever comes first. Chart abstractions will take place following discharge, death, or postoperative day 30 within a timeframe to be determined by the PI and site personnel. Data will be recorded on the Medical Record Review Form and entered into the online DMS. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

For each participating site, CCC staff at the University of Pennsylvania will over-read and re-abstract chart data for the first 3 randomized patients and additional charts as needed, as determined by the results of the initial chart review; for sites other than the University of Pennsylvania, charts will be photocopied and mailed via certified mail or scanned and emailed to the CCC. Sites will redact all personal identifying information prior to sending. Data will be re-abstracted by CCC staff and entered into the DMS for comparison to the chart abstraction results from individual sites. Following abstraction, photocopied or printed scans of charts will be disposed of in a locked cabinet and shredded. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

- *Medical record review (Date of surgery; anesthesia and surgery start and stop times; surgical procedure performed; intraoperative data including but not limited to estimated blood loss; fluids and blood products administered in the OR; intraoperative blood pressure and oxygen saturation; ASA physical status classification; initial anesthetic type; intrathecal agents administered (for patients receiving spinal anesthesia); documented level of arousability; peripheral nerve blocks performed; benzodiazepines and intravenous opioids administered in the OR; intraoperative adverse events including but not limited to cardiac arrest requiring CPR, anaphylaxis, aspiration;*

postoperative adverse events including but not limited to bleeding requiring transfusion; myocardial infarction, congestive heart failure, stroke or transient ischemic attack, pneumonia, urinary tract infection, wound infection, thromboembolic complications, unplanned intubation, prolonged mechanical ventilation, acute renal failure, cardiac arrest requiring CPR or defibrillation, epidural hematoma requiring surgical intervention, new permanent paralysis of the lower extremities, return to the operating room, inpatient falls, unplanned postoperative mechanical ventilation; additional surgeries performed; ICU utilization discharge destination; date of first ambulation; discharge status.)

Where relevant, data will also be abstracted from the chart regarding the timing and/or severity of specific complications or events, as well as causes of specific events as documented in the medical record.

6.3.4 60-day, 180-day, and 365-day interviews

Interviews for all patients will occur at approximately 60 days, 180 days, and 365 days after randomization. Interviews will be conducted centrally via telephone by trained CCC staff overseen by the study PI.

CCC staff will call patients and/or proxies using contact information obtained at the time of the baseline interview within the following assessment windows: between 30 and 90 days after randomization (for the 60-day interview); between 135 and 225 days after randomization (for the 180-day interview); and between 305 and 425 days after randomization (for the 365 day interview). The listings of patients due for follow-up will be generated by the study DCC and will be provided by the DCC to CCC personnel.

Patients or their proxies will complete a structured telephone interview. Additionally, where patients are providing their own responses to interview items, we will also conduct a brief interview with a proxy respondent (if available) during the same call to verify the patient's response regarding the primary outcome (i.e. degree of independence in ambulation). A proxy respondent or secondary contact (previously provided by the patient) may also be contacted regarding the primary outcome should the patient be unable to provide his/her own response at the time of the follow-up.

Participants who are unavailable at the time of the initial attempted contact will receive follow-up calls up to five to seven times weekly at variable times over the course of the assessment window; for non-respondents, CCC staff will place calls to secondary contacts and reminders will be sent via secure e-mail and registered mail where feasible to minimize loss to follow-up. For patients who cannot be reached within the assessment window for a particular interview, a letter approved by the IRB may be sent to the patient's and proxy's address providing CCC contact information and requesting phone contact with the patient and/or the proxy with a recommended window of contact. This process will be repeated once every 30 days until either contact is made, a total of 4 letters are sent, or 425 days have passed since the date of randomization. All letters will be sent using a method that confirms delivery, either United States Postal Service, FedEx, or a similar carrier. Choice of carrier will be at the discretion of the PI.

Calls will be made during business and evening hours of the patient's residence. Where feasible, calls will be audio-recorded with permission for quality assurance; audio files will be kept in digital format on media that will be stored in secure, locked cabinets within offices controlled by the PI when not in use. Audio files will be accessed for random auditing of interviews and additionally as needed for quality control by the study PI and CCC staff. When possible, the results of the follow-up interviews will be entered directly into the electronic study DMS via the 60, 180, and 365 Day Follow-up Forms and the 60 Day Proxy Interview for the Primary Outcome Form. Hard copy forms will be used in the event that study staff are unable to access the online DMS; data will be abstracted from hard copy forms by study staff into the online DMS and stored in secure locked cabinets within offices that are controlled by study personnel and locked when not in use.

- *Ambulation independence questionnaire*
- *Proxy ambulation independence questionnaire.*
- *Pain symptom questionnaire (pain with ambulation and at rest; pain medication usage)*

- *Mortality assessment*
- *Residential status assessment (i.e. residence at home, in a nursing home, etc…)*
- *WHODAS 2.0 (overall health and disability)*
- *Short Blessed Test (cognition)*

6.3.5 National death index search

A National Death Index (NDI) search will be performed during the final year of the study to obtain survival and cause-of-death data on all patients enrolled up to that point. The following patient-level variables will be submitted to the NDI to complete this search where available: first and last name, middle initial, social security number (complete or last 4 digits), month, day, and year of birth, race, sex, and state of residence. These data will be mailed to the NDI on an encrypted, password-protected CD-ROM or other appropriate digital media via certified overnight mail. No more than one individual will have access to transmitted data, and all transmitted patient-level data will be destroyed following the completion of the NDI search; no patient-level data will be retained at the CDC following completion of the NDI search.

NDI data will be transmitted from the US CDC's National Center for Health Statistics via password-protected encrypted CD-ROM or similar media to the CRCU or the CCC or DCC PI via overnight mail, and will be transferred directly to the DMS by CRCU staff. Following data transfer, the original NDI disk will be stored. Hard copy forms will be stored in a secure locked cabinet within offices controlled by study personnel and locked when not in use.

- *All-cause mortality*
- *Cause of death*

6.3.6 Medicare claims linkage

Permission will be sought from randomized patients who are Medicare beneficiaries to perform linkage of study data to Medicare claims once such claims are available and additional funding can be secured. Funding from the present grant will not be used to fund this linkage or related analyses; methods for data linkage, data management and analysis will be governed by a separate protocol.

6.3.7 End of Study Interview

Either the 180 day interview or the 365 day interview may represent the end of study interview depending on the timing of enrollment into the REGAIN trial and the availability of funding at the time of the scheduled interview.

6.4 Rescue Therapy

Management of all intraoperative events will be at the discretion of the treating anesthesiologist and surgeon based on clinical expertise and standard care.

6.5 Unscheduled Visits

No unscheduled visits will take place over the course of the study.

6.6 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the site Clinical Director for lack of adherence to study procedures or visit schedules, AEs, due to family preferences, or at the discretion of the treating physician. The site Clinical Director may also

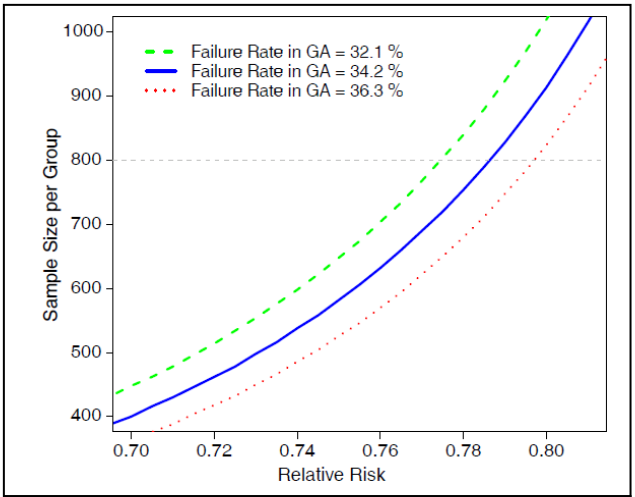

Figure 3. Sample sizes required for 80% power to detect a difference in the primary endpoint for patients randomized to spinal vs general anesthesia across a range of effect sizes.

withdraw subjects for administrative reasons. The date of withdrawal and any known reasons for withdrawal will be documented on the Subject Withdrawal Form and entered into the online study DMS.

6.6.1 Data Collection and Follow-up for Withdrawn Subjects

No attempts will be made to collect additional follow-up data from participants who have withdrawn consent.

7 Statistical Plan

Statistical analyses using datasets including identifiable patient data will be carried out on secure servers maintained by the Penn Clinical Research Computing Unit (see below); analyses will use standard statistical software such as R, SAS, and Stata.

7.1 Primary Endpoint

The primary endpoint for this study will be death or inability to walk 10 feet or across a room without human assistance at approximately 60 days after randomization. This endpoint will be analyzed as a binary outcome.

7.2 Secondary Endpoints

Secondary endpoints include both binary and continuous outcomes and will include but not be limited to:

- Inability to walk 10 feet or across a room without human assistance at 180 and 365 days
- Mortality (in-hospital, 60-day, 180-day, 365-day)
- Need for assistive devices for ambulation (60-day, 180-day, 365-day)
- All cause mortality (via NDI search)
- Cause of death (via NDI search)
- SBT score (60-day, 180-day, 365-day)
- WHODAS 2.0 score (60-day, 180-day, 365-day)
- Pain scores at rest and with movement (in-hospital, 60-day, 180-day, 365-day)
- New utilization of prescription pain medications (in-hospital, 60-day, 180-day, 365 day)
- Satisfaction with anesthesia care (in-hospital)
- Delirium (in-hospital), including presence of delirium and delirium severity score
- Major postoperative morbidity, including selected inpatient adverse events (in-hospital)

7.3 Sample Size and Power Determination

Power and sample size. Our sample size calculation is based on the primary outcome (inability to walk or death at 60 days). **Figure 3** shows sample size requirements for 80% power to detect a range of relative risks for this outcome between two randomized arms (α=0.05). The middle line shows the sample sizes required assuming a 34.2% rate of the primary outcome in the general anesthesia arm, (the rate observed in the 2,100-patient FOCUS trial);[78] the upper and lower lines show required sample sizes based on the FOCUS 95% confidence limits for this outcome (i.e., 32.1% and 36.3%). Our calculations assume a 5% loss to follow-up and a 5% crossover rate from spinal to general anesthesia.[102, 103]

Assuming that the primary outcome occurs in 34.2% of general anesthesia patients our planned sample will provide **80% power to detect a relative risk of 0.78** for this outcome among patients receiving spinal versus general anesthesia and **90% power to detect a relative risk of 0.76**. These effect sizes fall within the 95% confidence intervals for the effect of regional anesthesia on in-hospital mortality, pulmonary complications and postoperative confusion seen in prior retrospective studies[29, 52] and randomized trials,[26] and are of sufficient magnitude to justify changes in practice and policy; while smaller differences could exist, effects below this level would be unlikely by themselves to justify large-scale changes in anesthesia care. Additional power calculations indicate that the planned sample will have adequate power to detect clinically meaningful differences in secondary study endpoints, including survival, delirium, pain, overall health and disability, and changes in cognitive status over time.

7.4 Statistical Methods

7.4.1 Baseline Data

The distributions of analysis variables will be examined using tabular and graphical methods, such as histograms and boxplots, to identify outliers that may represent errors not captured by automated processes. Such values will be verified or corrected prior to analysis. Measures will be summarized using appropriate descriptive statistics, including means and standard deviations, medians, ranges, and proportions. Analyses will use commercial computing packages including SAS, Stata, and R.

7.4.2 Efficacy Analysis

All hypothesis tests will use a two-sided significance level (Type I error) of $\alpha = 0.05$. As the primary outcome (inability to walk or death at approximately 60 days) is binary, the primary analysis will compare the proportions of patients meeting this outcome between groups randomized to spinal versus general anesthesia using chi-square tests, stratified by site, gender, and fracture type. Secondary analyses will use multivariable logistic regression models to control for other covariates such as age, race, and baseline WHODAS 2.0 score. Similar approaches will be used to evaluate binary secondary outcomes, including mortality at approximately 180 and 365 days, return to the prior residence at approximately 180 and 365 days, occurrence of any major in-hospital complication, and binary pain, health/disability, and satisfaction endpoints.

For continuous endpoints such as overall WHODAS 2.0 score we will use analysis of variance (ANOVA) adjusted for age, gender, and fracture type. Further adjusted analysis will be performed using linear regression adjusting for potential covariate effects; normalization transformation may be considered if the normality assumption is violated. Standard regression diagnostics, including residual plots, and influence statistics will be used to identify outliers and examine the assumptions. We will provide in the analyses, in addition to tests of significance, confidence intervals for treatment effect, and various approaches to assess the robustness of the estimates to nuisance factors. (IR-6) Other continuous endpoints such as pain and satisfaction scores will be analyzed using similar methods.

Heterogeneity of Treatment Effects (HTE). For the primary outcome, analyses of treatment effects within pre-specified subgroups defined by: (1) fracture type; (2) gender; (3) pre-fracture level of overall disability; (4) pre-fracture disability in locomotion; (5) age category; (6) baseline cognitive status; (7) surgical procedure; (8) baseline pulmonary disease; (9) baseline cardiac disease; (10) nursing home versus non-nursing home residence prior to fracture. Subgroup comparisons will be conducted if any treatment-covariate interactions are at least suggestive ($p<0.20$; HT-3) and sample sizes and numbers of events within these subgroups are sufficient for analysis. Secondary outcomes also will be assessed for HTE. If there is a treatment difference together with evidence of heterogeneity, the relevant covariates and interactions will be added to the relevant regression models to see if an overall difference still exists. Additional pre-specified subgroup analyses will be performed for in-hospital delirium outcomes among patients for whom assessors were and were not blinded to treatment assignment.

7.4.3 Interim Analysis

As discussed in Section 8.6 below (“Stopping Rules”), we do not plan to perform interim analyses to test for superiority or inferiority of either study regimen with regard to any of the primary or secondary study outcomes.

7.4.4 Safety Analysis

Randomized subjects will have information collected on defined safety endpoints as described above in Section 4.2.3. (“Primary Safety Endpoints”) The overall study safety analysis will assess the rate of all combined safety as well as the rates of individual safety events. Reviews of safety data will be performed after the enrollment of the first 100 patients, and after accrual of 25%, 50%, and 75% of the study sample.

Reviews of safety data will be carried out by the DSMB, the PI, and other appropriate CCC and DCC leadership.

7.5 Subject Population(s) for Analysis

- All-randomized population: The main analysis for the primary outcome will include the all-randomized population; this population will also be used for the main analysis of selected secondary outcomes including mortality, major intraoperative and postoperative adverse events, WHODAS 2.0 score, SBT score, pain at motion and at rest, satisfaction with care, location of residence, and severity of delirium as assessed by 3D-CAM.
- Per-protocol population: Secondary analyses for all of the above named-variables will restrict the population under consideration to patients who received the initial anesthesia type (i.e. spinal or general anesthesia) to which they were randomized
- Randomized patients without delirium at baseline: Patients for whom delirium is present prior to randomization will not be eligible for inclusion in analyses that examine a binary endpoint indicating the presence or absence of new postoperative delirium. As such, this analysis will include randomized patients without a baseline diagnosis of delirium prior to randomization.
- Randomized patients living at home prior to fracture: Patients not living at home prior to fracture will not be eligible for inclusion in analyses that examine the percentage returning to home at 60, 180, and 365 days. As such, this analysis will include only randomized patients living at home prior to fracture.
- Randomized patients not requiring assistive devices for ambulation at baseline: Patients for whom assistive devices were required for ambulation prior to fracture will not be eligible for inclusion in analyses that examine binary endpoints indicating whether such devices are required for ambulation after fracture. As such, this analysis will include randomized patients without a requirement for assistive devices for ambulation prior to fracture.
- Randomized patients without cognitive dysfunction at baseline: Patients for whom cognitive dysfunction is present prior to randomization will not be eligible for inclusion in analyses that examine a binary endpoint indicating the presence or absence of new cognitive dysfunction at 60, 180, or 365 days. As such, this analysis will include randomized patients without cognitive dysfunction, as defined by SBT score, prior to randomization.
- Randomized patients not requiring prescription pain medicines at baseline: Patients for whom prescription pain medicines are required for pain control prior to fracture will not be eligible for inclusion in analyses that examine a binary endpoint indicating the presence or absence of new need for prescription pain medicines at 60, 180, or 365 days. As such, this analysis will exclude randomized patients reporting use of prescription pain medicines prior to fracture.
- Additional outcome-specific subpopulations: Additional sub-populations will be defined at the time of analysis as required for appropriate secondary analysis of key study endpoints.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events.

8.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal

- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious will be regarded as **non-serious adverse events**.

8.2 Recording of Adverse Events

At each contact with the subject and at the time of hospital discharge, study personnel will seek information on adverse events by specific questioning and, as appropriate, by examination and medical record review. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events identified during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be determined by an adverse event review committee as being definitely related, probably related, possibly related, unlikely to be related or unrelated to the study intervention or other study procedures. For purposes of making determinations of relatedness, members of the safety monitoring committee may have access as needed to relevant intraoperative, preoperative, and postoperative data; additional identifying data not required for determinations of relatedness will be suppressed. If needed for determinations of relatedness, unblinding with regards to treatment assignment will be permitted at the level of the individual case. The safety monitoring committee will include 2-3 members and will be led by the PI or their designate.

8.4 Reporting of Adverse Events and Unanticipated Problems

At each contact with each subject, the study staff will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in appropriate case report forms. All clearly related signs, symptoms, and abnormal diagnostic procedure results will be documented.

Initial reports will be submitted as narratives to the PI office; the minimum necessary information to be provided at the time of the initial report will include:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies.

8.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the site Clinical Director's or PI's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The Clinical Director will be responsible for ensuring that all SAE are followed until either resolved or stable.

8.4.2 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to the Clinical Coordinating Center by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the site Clinical Director and submitted to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and/or email to:

Mark David Neuman, M.D., M.Sc.
Study Director, REGAIN Trial
University of Pennsylvania
308 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104
Office: (215) 746-7468
Cell: (215) 760-7471
Email: mark.neuman@uphs.upenn.edu

Within the following 48 hours, the site Clinical Director will provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This will include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events will be provided promptly to the study sponsor.

8.4.3 Investigator Reporting: Notifying the IRB

Reports of the following problems will be reported to the Penn IRB and other appropriate site IRBs within 10 working days from the time the investigator becomes aware of the event:

Any adverse event that occurs any time during or after the research study, which in the opinion of the principal investigator is:

- **Unexpected** (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

- **Related** to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

The above is required regardless of whether the event is serious or non-serious, on-site or off-site.

Protocol Deviations
Any protocol deviations initiated without Sponsor and/or Penn IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, will be reported to the Sponsor and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

Reporting Process
Unanticipated problems as defined above will be reported to the Penn IRB using the appropriate CRF or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the PI's office.

Other Reportable events:
The following events will also be reported to the Penn IRB:

- Any adverse event that would cause the modification of the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency, such as:
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.4.4 Sponsor reporting: Notifying participating investigators

Investigators at participating sites will be notified by the CCC of any of the above adverse events or findings to participating investigators based on the same timing as required for IRB reporting described above.

8.5 Unblinding Procedures

Where feasible based on staff availability and site resources, some sites may conduct blinded assessments for in-hospital outcomes. As at least one study team member at each site will be unblinded to treatment assignment, no unblinding procedures are proposed for the REGAIN trial at the level of the individual site.

Assessments of aggregate data related to patient characteristics and study outcomes will occur in a blinded fashion such that investigators cannot determine subject randomization assignment; unblinding at the level of the individual patient will be permitted as needed for making determinations of relatedness for adverse events (see section 8.3 above). Unblinding with regard to randomization assignment for the full study sample will occur at the end of study enrollment, or prior to that point as per the determination of the Principal Investigator based on the input of the DSMB and/or the study sponsor.

8.6 Stopping Rules

Spinal and general anesthesia are universally accepted as standard care practices for hip fracture surgery. There is no known or expected difference in overall risk or safety to patients between these two approaches. For this reason, we do not propose formal stopping rules based on demonstrated superiority or inferiority of either treatment with regard to the primary or secondary endpoints.

8.7 Medical Monitoring

The site Clinical Director will oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

8.7.1 Data and Safety Monitoring Plan

Data and safety monitoring will be the responsibility of the Study Director/PI (Neuman), the study Biostatistician, site Clinical Directors, and a Data Safety Monitoring Board (DSMB).

Data Safety Monitoring Board
The DSMB roles, responsibilities, and operating procedures are defined by the REGAIN DSMB Charter; this charter will be initially drafted by the REGAIN CCC and DCC leads and will be modified and ratified by the DSMB prior to the initiation of subject recruitment. The DSMB will be composed of 5-7 patients, physicians, and investigators who are not involved in the conduct of the study in any way; who do not have subordinate relationships with the PI or any member of the study team; and who are qualified through other experience or training to review the clinical and research data from the study. The selection of the DSMB according to these criteria will enable the protection of subjects and the integrity of the data through a group which is sufficiently objective yet clinically qualified to fulfill the role. The DSMB will be unblinded to subject treatment assignment.

DSMB Standard Operating Procedures
The DSMB will be identified by the PI (Neuman), the Biostatistician, and/or the funding sponsor, and will be invited to serve in this capacity until the conclusion of the study. The DSMB will meet prior to the initiation of enrollment to review the protocol, the DSMB charter and reporting templates. Subsequent DSMB meetings will review the protocol, safety and adverse event data, available outcome data, and information on subject accrual and protocol compliance; these meetings will take place within 1 month of the time of planned interim safety event analyses, which will occur after randomization of the first 100 patients and after randomization of ¼, ½, and ¾ of the total planned randomized sample of 1,600. The study team will prepare all documents and reports in such a manner as to allow complete understanding of the study and the results, and will provide the DSMB with the materials in advance of their meeting date, which will scheduled by the DSMB at their convenience. As appropriate, the DSMB may consider recommending for protocol modifications or revisions to the informed consent document if problems with enrollment, accrual, or protocol implementation are identified, or if identified safety events are noted to occur at a rate beyond that which would be expected to occur in the course of standard care based on available research and clinical experience.

Study enrollment and follow up visits will continue during the period of DSMB review and will proceed until study completion unless the sponsor or the PI determines stopping the study is necessary prior to the conclusion of the study.

9 Study Administration, Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial as appropriate and applicable to the study.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. Data will be collected using CRFs developed specifically for the REGAIN trial as well as standardized instruments. Forms will be made available for completion on paper as well as directly into the electronic data management system. Data will be collected from in-person and telephone interviews with study participants and their proxy, and from clinical information contained in medical records. When possible during the follow-up phase of telephone interviewing, data collected by the CCC will be entered directly into the electronic data management system. Hard copy CRFs will be available in case of DMS inaccessibility.

9.4 Data Collection and Management

Data Collection Procedures. All data collection procedures for the REGAIN Trial are outlined above in **Section 6** ("Study Procedures")

Data management procedures. The Data Coordinating Center (DCC) at the University of Pennsylvania will develop a data management system for the collection, validation, storage and management of trial data. The data management system will use a combination of tools to perform the following study functions:

- Subject tracking – to monitor screening and enrollment and produce subject visit schedules
- Eligibility determination and randomization - to evaluate screening data to determine eligibility and randomize subjects according to the randomization schema provided by the Biostatistician
- Comprehensive data collection modules to accommodate all types of trial data

Data management system. All research data for this trial will be stored in an electronic database that is managed by the Clinical Research Computing Unit (CRCU) of the University of Pennsylvania Center for

Clinical Epidemiology and Biostatistics (CCEB). The database will be hosted on secure computing servers and will be restricted to only those individuals who are authorized to work on the trial. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies.

The DMS will exist within an appropriate database structure to support the requirements of the DMS and to promote data security and integrity. Electronic audit trails of changes to database contents will be incorporated into the design and will capture and record those changes automatically. In addition to the trial database where actual results will be maintained, a development database will be created. The development database is a working environment that facilitates the development, testing, troubleshooting, enhancement, and training for the DMS without adversely affecting the integrity of the collected project data.

CRCU servers exist within highly secure computing environments of the CCEB that are the responsibility of the Penn Medicine Academic Computing Services group. This group focuses on providing hardware and software services, systems administration, business continuity, and security services to research projects within the CCEB and other departments in Penn Medicine.

Data Security Measures: The research computing environment has a security component required due to HIPAA; federal, state, and research compliance regulations; and CCEB best practices for safeguarding research data. The CCEB secures its logical network using virtual private network (VPN) protocols and network address translation (NAT) protocols layered on top of the single logical virtual local area network (VLAN). The VPN protocols provide encrypted “data in motion” protections and “fire-walled” connections between each of the physical network segments of the logical network. Applying VPN/VLAN encrypted connections allow all internal CCEB data to “tunnel through” and traverse the University’s physical networks as needed, while maintaining security at the logical CCEB network level, thus ensuring the privacy of the CCEB data and the availability of the data to only CCEB managed resources and users.

In addition to the VLAN and VPN technologies, the CCEB network utilizes the NAT protocols to provide private network addressing within the logical CCEB network. This additional precaution ensures that all network protocols running into or out of the logical CCEB network are essentially “proxy” connections that are only passed through one of several CCEB firewall devices. Providing a proxy service allows the CCEB to monitor, log and control all data and network protocols coming into and going out of its logical network.

The physical building environment for supporting the computing environments required by the CRCU is co-located within a formal data center facility that is managed by University of Pennsylvania; Penn Medicine and Information Systems and Computing personnel. The data center also has uninterrupted power supply (UPS)/diesel subsystems to ensure that adequate and constant electrical power requirements are met at all times, even during prolonged power outages. The data center has secured and limited physical access and is constructed with walls and doors to prevent break-through efforts and/or illegal entry.

Data entry. The CRCU will configure a remote data capture (RDC) module to allow remote data entry from the participating trial sites. The RDC module will be available to any computer with a persistent internet connection and will be run using standard web browser software. The data entry screens will look like the data collection forms as closely as possible to allow visual referencing during data entry, enhancing accuracy and efficiency. Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and skip pattern enforcement. This data entry module will be configured for single data entry.

NDI data will be transmitted from the US CDC's National Center for Health Statistics to CRCU staff or to the DCC or CCC PI via password-protected encrypted CD-ROM or similar media by overnight mail, and will be loaded directly onto the DMS. Following data transfer, the original NDI disk will be stored in a locked safe or secure locked cabinet within the CRCU.

Data Quality Module: The CRCU will configure a module to assess data entered in to the database in relation to a set of rules that describe expectations for those data items. This set of data validation rules will be defined by CRCU clinical data management personnel and the study PI and Biostatistician to identify data items that may have been collected incorrectly or entered into the database inaccurately. The module will run automatically to inspect all newly entered or modified data. Clinical site personnel will review the results of the data validation and take any required corrective action for invalid data. Queries will be recorded and tracked in the data quality module. Corrections identified for individual data items will be managed by the clinical sites. All changes made will be recorded in an electronic audit trail and documented using change control procedures.

The DCC and CCC teams will establish specific training and certification procedures to ensure that all study personnel are well trained in the performance of study procedures, data collection and data entry processes

A Manual of Procedures (MOP) will provide detailed instruction for the performance of screening, enrollment, randomization and follow-up procedures. The MOP will provide instruction in case report form completion, and use of the electronic data management system,

Reports Module: The CRCU will develop a set of standard reports to clearly illustrate the results of trial recruitment efforts and study events, and to document any safety concerns that have occurred during the study. Additional reports may be developed where regular feedback is desirable. Such additional reports may include data entry timeliness and data quality assessments.

9.5 Management of audio recordings of 60, 180, and 365 day interviews:

All post-discharge telephone interviews will be audio-recorded with permission for quality assurance; audio files will be kept in digital format on removable media (e.g. Flash Drive, DVD-ROM) that will be stored in secure, locked cabinets within offices controlled by the PI when not in use. Audio files will be accessed for random auditing of interviews and additionally as needed for quality control by the study PI and CCC staff using PCs located within offices controlled by the PI.

9.6 Records retention

All investigators will retain study essential documents for at least 7 years after the last subject completes the study, or longer if recommended by the IRB, the DSMB or another oversight organization within or outside the University of Pennsylvania.

9.7 Public access plan

A complete, cleaned, de-identified copy of the final dataset used in conducting the final analyses will be made available within one year after completion of the study. The CRCU will remove any patient, site, or other sensitive information from the final database to make it suitable for scientific use. This includes removal of all Personal Health Information (PHI) and indirect identifiers that are not listed as PHI but could lead to "deductive disclosure" such as comment fields and site numbers. Study specific de-identification methods will be documented in the final protocol. Documentation regarding the data and relevant study details will be provided. This includes the annotated case report form (CRF); a text file outlining the structure, variables and contents of each dataset. The study documentation for this trial will include the final protocol, study procedures, data collection forms, descriptions of all variable recoding performed, and a list and links to all primary publications. Datasets and accompanying files will be available on request from the PI or DCC; key datasets will be archived as appropriate to ensure their long-term value and usability.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according a formal monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities, and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The PI will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

11.1 Risks

(1) Risk of Randomization. As treatments will be assigned randomly, the process of randomization will necessarily carry the associated risks and benefits of the specific type of anesthesia to be used here. Both anesthetic regimens to be used in this study are standard of care, with risks and benefits described below;

(2) Anesthesia Regimens. Risks for participation in this study do not go beyond those risks typically associated with spinal or general anesthesia as used in routine care. Medications typically used for general and regional anesthesia (spinal block) are FDA approved to be used alone and in combination for anesthesia. Beyond the study consent, patients will also undergo standard procedural consent to discuss the risks and benefits of regional and general anesthesia as per the routine of the local hospital. Risks associated with spinal anesthesia: Occasionally, regional anesthesia does not provide sufficient pain relief. In these situations, he/she may receive general anesthesia or intravenous pain-relieving drugs to supplement regional anesthesia. The risks of regional anesthesia include, but are not limited to, low blood pressure, itching or allergic reactions to drugs, obstruction or cessation of breathing, headache, and very rarely temporary paralysis, nerve injury, infection or meningitis. Risks of general anesthesia include, but are not limited to, nausea and vomiting, awareness under anesthesia, damage to lips or teeth, sore throat, headache, eye injury or blindness, infection, transfusion reactions (including excessive bleeding and kidney damage), drug reactions (including rash, shock, and cardiac/respiratory arrest), blood clots, lung infections, loss of sensation or limb function, paralysis, stroke, or brain injury, heart failure or heart attack, and death. Patients will have been screened by both their surgical and anesthesia team for allergies to any medications including those commonly used for anesthesia and post operative pain control;

(3) Confidentiality breaches. Risks of breaches of confidentiality are small but nonetheless possible. However, all possible efforts have been taken to ensure the security of study data and minimize the risks of accidental disclosure of identifiable data elements, as outlined below.

11.2 Benefits

At present, insufficient evidence exists to characterize the comparative effectiveness of spinal versus general anesthesia for hip fracture surgery among older adults; if a relative difference in comparative effectiveness between these two modalities of anesthesia is found in the present study, the potential exists that direct benefits of participation could accrue to those patients randomized to a given study arm who may have otherwise received a different type of anesthesia. However, research participants may also receive no direct benefits from participation in this study. For individuals other than the study participants, the present study has substantial potential to yield benefits to individuals with hip fractures. As stated above, gaps in knowledge regarding the comparative effectiveness of regional versus general anesthesia for improving patient-centered outcomes after hip fracture currently limits efforts to improve quality in hip fracture care and has been identified as a key area for hip fracture research by a range of stakeholder groups. Our study will address these gaps in knowledge through the first adequately-powered prospective study to compare the impact of spinal vs general anesthesia for hip fracture surgery on patient-centered outcomes. Given the use of established and conventional anesthesia treatments in both arms of the study, and the potential for this study to benefit a large number of patients with hip fracture, we judge the risks to study subjects to be reasonable in relation to the anticipated benefits to research participants and others.

11.3 Risk/Benefit Comparison.

Based on the considerations listed above, the study could be considered greater than minimal risk to patients. However, the knowledge that may be gained from the present study may impact the care of over 300,000 individuals in the US each year and 1.6 million worldwide. Hip fracture represents a critical public health concern for older individuals and their families; identification of evidence-based treatments that may improve functional and survival outcomes after hip fracture is critical for improving the quality of hip fracture care and reducing the massive burden of death and disability attributable to hip fracture. Moreover, decreasing the burden of disability associated with hip fractures may have positive effects on health care resource use among hip fracture patients. By comparing the effectiveness of two widely used approaches to anesthesia care for hip fracture surgery, the present study has the potential to yield a transformative impact on how hip fracture care is delivered in the US and other countries. Given these considerations, the risks to the study subjects, which will be fully disclosed, and managed and mitigated to the maximum extent possible through appropriate study procedures and supervision, are reasonable in relation to the importance of the knowledge that may result from this study.

11.4 Informed Consent Process / HIPAA Authorization

The site PI, the site Clinical Research Coordinator, or another member of the orthopedic or anesthesia team will obtain informed consent and HIPAA Authorization prior to randomization. The patient will learn about the purpose of the study, the study anesthesia regimens, and data collection procedures and timing at the time of informed consent. For consenting patients, a note will be written in the chart to indicate completion of consent.

Some patients may be too sick or not competent to give permission to enter the study. In these cases, we will attempt to recruit the patient by seeking permission of the family or caregiver who is signing informed consent for the surgical procedure. We believe it is appropriate and ethical to recruit these patients into the trial because these patients are commonly treated with both general and spinal anesthesia in practice. Extrapolation of the results from a study excluding seriously ill or cognitively impaired patients may be unreliable so it is important that direct evidence be obtained by including such patients in the study. For subjects for whom proxy consent is initially obtained, but the patient regains the ability to control medical decisions for themselves by postoperative day 3 or the day of hospital discharge (whichever comes first), direct written consent will be obtained. For subjects who decline participation at this point, no further data will be collected; data collected prior to this point will be retained as per the data management and analysis plan outlined above.

For otherwise eligible patients who decline participation, reasons for refusal will be documented.

12 Study Finances

12.1 Funding Source

This study is funded through a contract with the Patient Centered Outcomes Research Institute (Washington, DC)

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the applicable University conflict of interest policy(ies).

12.3 Subject Stipends or Payments

No stipends or payments will be provided to study subjects.

13 Publication Plan

The results of this study in whole or in part will be prepared and submitted for publication to professional meetings and/or journals in order to disseminate the information gleaned from this investigation. Subject data will be published in aggregate and will be deidentified prior to analysis in order to protect the confidentiality of study participants.

The publication of study reports will be governed by the REGAIN Publication Policy, which will be developed by a committee to include the PI and selected other investigators. Policies on authorship will be determined by committee vote, and will be consistent with available standards and norms regarding authorship on scientific publications for multicenter randomized trials.

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REGAIN REGIONAL VS. GENERAL ANESTHESIA FOR PROMOTING INDEPENDENCE AFTER HIP FRACTURE SURGERY

Protocol #: 822632

Protocol Title: A Randomized Controlled Trial of Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN Trial)

PI: Mark D. Neuman, MD, MSc

	Version No.	Version Date
Current Approved Protocol	2.2	August 22, 2015
Amended Protocol	2.3	March 29, 2016

SUMMARY OF CHANGES

Title Page

- Correction of typo on PI address.

Page 14, Section 6.3.3: Post-discharge medical record review

- Added additional method for sending charts for re-abstraction. This was included to provide sites with an option for a more efficient method of document transfer.
- Clarified that charts sent to CCC will be de-identified by the site prior to sending

Page 15, Section 6.3.4: 60-day, 180-day, and 365-day interviews

- Added sentence regarding contacting proxy or secondary contact. This was included to clarify that a subject's proxy or secondary contact will be interviewed if the subject is unable to provide his/her own response.

Page 28, Section 11.4: Informed Consent Process/HIPAA Authorization

- Deleted end of sentence. This was removed because a separate consent and study protocol enabling the collection of more than a subject's reason for refusal does not currently exist.

Administrative Changes

- Updated protocol version number and date throughout the document.