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Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): protocol for a pragmatic, international multicenter trial

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ABSTRACT

Introduction: Hip fractures occur 1.6 million times each year worldwide, with substantial associated mortality and losses of independence. 95% of hip fracture patients undergo surgical treatment, and the most common types of anesthesia used for hip fracture surgery are general anesthesia and spinal anesthesia. While some studies have suggested short-term outcome benefits with spinal anesthesia versus general anesthesia, these proposed benefits have not been tested in a large-scale, high-quality trial, nor have these anesthesia options been compared with regard to longer-term patient-centered outcomes.

Methods: The REGAIN Trial (Regional versus General Anesthesia for Promoting Independence after Hip Fracture) is an international, multicenter, pragmatic randomized controlled trial. 1,600 previously ambulatory patients aged 50 and older will be randomly allocated to receive either general or spinal anesthesia for hip fracture surgery. The primary outcome is the return of ambulatory ability (i.e. ability to walk 10 feet or across a room) at 60 days after randomization, which will be assessed via telephone interview by staff who are blinded to treatment assignment. Secondary outcomes will be assessed by in-person assessment and medical record review for in-hospital endpoints (delirium; major inpatient medical complications and mortality; acute postoperative pain; patient satisfaction; length of stay) and by telephone interview for 60-, 180-, and 365-day endpoints (mortality; disability-free survival; chronic pain; return to the pre-fracture residence; need for new assistive devices for ambulation; cognitive impairment).

Ethics and dissemination: The REGAIN trial has been approved by the ethics boards of all participating sites. Recruitment began in February 2016 and will continue until the end of 2019. Dissemination plans include presentations at scientific conferences, scientific publications, stakeholder engagement efforts, and presentation to the public via lay media outlets.

Registration details: The study is registered at clinicaltrials.gov, NCT02507505 (last updated June 20, 2016).

Trial registration number: NCT02507505

STRENGTHS AND LIMITATIONS OF THIS STUDY

- REGAIN will evaluate outcomes of common anesthesia techniques for hip fracture surgery, an event that occurs over 1.6 million times each year world-wide, through an international, multicenter, randomized trial.
- Pragmatic, "real-world" treatment protocols are reflective of current practice and will allow the results to be generalized across a range of care settings.
- Collection of patient-centered outcomes data, including measures of functional independence, at up to 1 year will provide insight into the relationship between the study intervention and meaningful patient endpoints.
- Input by patients and stakeholders at each stage will improve translation and dissemination of eventual results to affected communities.
- Data collection for certain in-hospital adverse events will rely on medical record review; as such, events that are not recorded in the medical record may not be captured.

INTRODUCTION

Over 1.6 million hip fractures occur each year worldwide, with major consequences for the individual and society.[1 2] Within 12 months of fracture, 25% of patients die,[3 4] and half of previously community-dwelling patients either die or require new nursing home admission.[5] Hip fractures create substantial needs for informal caregiving [6 7] and post-acute and long-term care involving major costs to society;[8] the estimated costs attributable to hip fractures in the US exceeded $12 billion in 2005 and will exceed $18 billion by 2025.[9]

Nearly all patients with hip fractures undergo surgical treatment. Anesthesia for hip fracture surgery varies widely in practice,[10 11] with general anesthesia and spinal anesthesia representing the two most common approaches.[12] Available studies comparing outcomes with spinal versus general anesthesia for hip fracture surgery have been reviewed elsewhere.[13-17] While spinal anesthesia has been theorized to improve outcomes by avoiding the need for intubation and exposure to general anesthetics, available randomized studies have yielded equivocal findings regarding the relative superiority of one technique over the other with regard to either short-term morbidity and mortality or longer-term functional recovery.

Existing randomized studies are characterized by major shortcomings. A 2016 Cochrane review of trials comparing spinal versus general anesthesia for hip fracture surgery between 1977 and 2012 rated the quality of available evidence as “very poor” for all outcomes studied.[13] 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 that the available evidence “is old and does not reflect

current practice."[18] In particular, few data are available to characterize the impact of anesthesia technique on patient-centered outcomes, such as functional recovery or satisfaction.

Study objectives

The REGAIN trial (Regional versus General Anesthesia for Promoting Independence after Hip Fracture) will evaluate the effect of spinal versus general anesthesia on recovery of ambulation at 60 days after randomization (primary outcome) and other patient-centered outcomes measured at up to one year. Our primary hypothesis is that patients who receive spinal anesthesia will demonstrate improved ambulation at 60 days after randomization compared to patients who receive general anesthesia.

METHODS AND ANALYSIS

Study design. We will perform a randomized, multicenter, pragmatic active comparator study of two standard care approaches to anesthesia for hip fracture surgery (i.e. spinal and general anesthesia). 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. The primary outcome will be assessed at 60 days after randomization by a telephone interviewer blinded to treatment assignment.

Pragmatic design features of the REGAIN trial. The development process for the REGAIN Trial protocol engaged patients, stakeholders, researchers, and clinicians to develop a pragmatic study design that would yield findings with relevance to clinical practice across a range of settings. We used the PRECIS tool[19] to formalize the implications of specific design choices for the nature of the REGAIN trial as a pragmatic (effectiveness) trial versus an explanatory (efficacy) trial (**Table 1**) across a range of domains.

Eligibility criteria appear in **Box 1.**

Baseline assessment. As shown in the study assessment schedule (**Table 2**), enrolled patients will undergo a pre-randomization assessment that includes a medical history questionnaire, a brief medical record review, and selected assessments to assess: (1) baseline disability, as measured by the 12-item World Health Organization Disability Assessment Schedule, version 2.0 (WHODAS 2.0), a validated patient-reported outcome that assesses cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society;[20 21] (2) baseline cognitive status, as measured by the Short Blessed Test, a well-validated brief cognitive screening tool;[22 23] (3) delirium, as measured by the 3D-CAM a well-validated brief assessment tool with high sensitivity and specificity for delirium;[24 25](4) pre-fracture pain symptoms, as measured by items adapted from the Brief Pain Inventory;[26 27] and (5) resilience, as measured by the Brief Resilience Scale, a short, validated tool measuring an individual's ability to "bounce back" from a stressful event.[28] We will collect contact information for the patient and for alternate contacts as required for telephone follow-up. In patients who agree to provide these data, social security numbers and Medicare beneficiary identifiers will be collected for relevant database linkages.

Interventions. We will randomly allocate patients to receive standard care spinal anesthesia or standard care general anesthesia. Apart from the decision regarding the primary anesthetic technique (spinal versus general anesthesia), all decisions about pre-operative, intraoperative, and post-operative care will be made by the clinical care team.

The intervention will occur by providing the treating clinical anesthesia staff written instructions (**Box 2**) directing them to perform a standard care spinal anesthetic or a standard care general

anesthetic. For patients who are randomized to receive spinal anesthesia, instructions will be provided to rate the level of sedation in the anesthetic record at least once between induction and emergence on a scale of 1 (deep sedation) to 5 (alert) based on the arousability subscale of the Observer's Assessment of Alertness/Sedation scale.[29]

Outcomes

Primary outcome: Independence in walking at 60 days after randomization. The primary outcome will be assessed by telephone interview at 60 days after randomization. This assessment will be conducted centrally by the study Clinical Coordinating Center at the University of Pennsylvania. Assessments will be conducted by staff who will be blinded to treatment assignment. 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. For patients who are unable to provide their own responses, available secondary informants will be interviewed regarding the participant's ability to walk independently at 60 days.

The primary outcome for REGAIN was selected based on consultation with patient and stakeholder partners as a clinically meaningful measure that also predicts key long-term outcomes. Data from the Baltimore Hip Studies indicate that patients who were unable to walk at 60 days demonstrated high rates of persistent inability to walk at one year (OR 11.1, 95% CI 6.6-18.7), one year mortality (OR 3.6, 95% CI 1.9-6.5), and new nursing home placement at one year (OR 6.2, 95% CI 3.9-9.7) compared to those who could walk independently at 60 days.[30]

Secondary outcomes (in-hospital): (1) Postoperative delirium will be assessed by study staff prior to randomization and daily up to postoperative day 3 or the day of discharge (whichever occurs first) via the 3D-CAM;[24 25] (2) acute postoperative pain will be assessed by study staff via

in-person interview daily up to postoperative day 3 or the day of discharge (whichever occurs first) via items adapted from the Brief Pain Inventory;[26 27](3) satisfaction with anesthesia care will be assessed on postoperative day 3 or the day of discharge (whichever occurs first) via the Bauer Patient Satisfaction Questionnaire;[31] (4) inpatient mortality and major inpatient morbidity will be assessed via chart review by site staff using standardized outcome definitions following hospital discharge, death, or at 30 days after surgery, whichever occurs first. To increase the feasibility of trial implementation across sites with varied staffing capabilities, we will encourage but not require those staff who assess in-hospital endpoints to be blinded to treatment assignment.

Secondary outcomes (post-discharge): Secondary outcomes will be collected via telephone interview by blinded study staff at 60, 180, and 365 days after randomization. Secondary outcomes will include: (1) overall health and disability, as assessed via telephone interview with patients or proxies via the WHODAS 2.0;[20 21] (2) chronic pain, as assessed via two adapted Brief Pain Inventory items to assess the extent of pain at worst and on average over the past 7 days. (3) cognitive function, as assessed by the Short Blessed Test;[22 23] (4) independence in locomotion and need for assistive devices for walking (i.e. cane, walker), and (5) location of residence (i.e. home versus nursing facility). Finally, vital status will be assessed via patient and/or proxy telephone interview at approximately 60, 180, and 365 days after randomization and via a National Death Index (NDI) search for US patients in the final year of the study.

Sample size planning

The REGAIN trial will randomize 1,600 patients to spinal versus general anesthesia for hip fracture surgery. Assuming a 34% rate of the primary outcome (death or new inability to walk at

60 days) in the general anesthesia arm (the rate observed in the 2,000-patient FOCUS trial),[32] this sample will provide 80% power to detect a relative risk of 0.78 for the primary outcome among patients receiving spinal versus general anesthesia and 90% power to detect a relative risk of 0.76 at an alpha value of 0.05. Sample size calculations allow for 5% loss to follow-up for the primary outcome and a 5% crossover rate from spinal to general anesthesia.[33 34]

The planned sample will also provide sufficient power for testing of hypotheses related to secondary outcomes. In terms of overall health and disability, a change of 8 points or greater represents a clinically important difference for the WHODAS 2.0;[20] the WHODAS 2.0 standard deviation among adults aged 75-85 with more than one chronic physical condition is 15.8%.[35] Given these assumptions our sample will provide over 99% power to detect a clinically significant difference in disability at 180 days between groups.

Recruitment

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 for their patients to be enrolled. For potentially eligible patients, a member of the REGAIN research team will approach the patient and/or their legally authorized representative (based on local IRB guidance) between the time of diagnosis and the time of surgery to explain the study, complete a brief screening evaluation, and obtain written informed consent. For patients who are too sick or who are not competent to give their own permission to enter the study, consent will be obtained from the patient's legally authorized representative if permitted by the local IRB.

REGAIN recruiting sites have been selected to represent a broad range of geographic locations and practice settings in the US and Canada, including large teaching and non-teaching hospitals and smaller community facilities. The site selection process for REGAIN included consideration of annual hip fracture volume, presence of buy-in from clinical leaders, research infrastructure, and past experience with randomized trials.

Allocation

Randomization will be carried out on the day of surgery immediately prior to start of anesthesia care and will be performed centrally through an online electronic data management system. Site research staff will obtain the randomization assignment from the data management system web portal and will communicate the treatment assignment to the anesthesia team on the day of surgery. Participants will be randomly assigned to one of the two treatment regimens in a 1:1 ratio. For each arm, balanced randomization of subjects, stratified by site, sex, and fracture type (intracapsular versus extracapsular), will be achieved by permuted block randomization with variable block sizes.[36 37]

Data analysis and management

Both primary and secondary outcomes will be evaluated under the intention-to-treat principle. All hypothesis tests will be performed using a two-sided significance level (Type I error) of $\alpha = 0.05$. Sensitivity analyses using the actual treatment received (rather than assigned) will be performed and compared with the intention-to-treat analysis results; additional sensitivity analyses will assess the potential impact of missing data due to losses to follow-up.

The primary analysis will compare the proportions of patients who can walk independently at 60 days between groups randomized to spinal versus general anesthesia using the Mantel-Haenszel

tests, stratified by site, gender, and fracture type. The Mantel-Haenszel odds ratio will be reported. Stratum-specific odds ratios will be generated and tested for homogeneity across strata using the Breslow-Day test.[38] If the result is significant, separate odds ratios for each stratum will be reported.

The ability to walk independently at each time point (60, 180, and 365 days) will be analyzed using multivariable logistic regression models that control for other covariates, including stratification factors (site, gender, and fracture type), and baseline variables that have potential association with the outcome, with particular attention to any such variable that appears imbalanced between treatment groups. Generalized linear mixed models will be used to perform a repeated measures analysis, looking at the ability to walk at 60, 180, and 365 days. We will use residual (or restricted) maximum likelihood methods for parameter estimates and significance testing. A function of time and the covariates mentioned above will be included as fixed effects in the regression.

The analytical approaches specified for the primary outcome will also be used for the binary secondary outcomes, including need for assistive devices for walking, postoperative delirium, mortality, return to the prior residence, occurrence of any major in-hospital complication. Continuous secondary outcomes including WHODAS 2.0 score, pain scale values, cognitive function score, and patient satisfaction scores will be compared between treatment groups using analysis of variance adjusting for the above stratification factors.

Missing Data. We will evaluate the amount, reasons for and patterns of missing data, with a particular attention to the lost-to-follow-up data, in primary and secondary outcomes. Primary and secondary analyses will assume missing values are "at random," relative to other data that we have collected; if the reasons for missing values suggest that the missingness is

"nonignorable" (i.e. not at random), we will develop models for missingness (for example, a selection model where the risk for drop-out depends on some clinical response) and use these models to help us assess the potential impact of missing data on our results.[39 40] We will also do a "worst case scenario" sensitivity analysis, i.e., all missing 60-day values in one treatment group will be replaced with the worst outcome and those in the other group with the best outcome.

Heterogeneity of treatment effects. Subgroup comparisons will be conducted if any treatment-covariate interactions are at least suggestive ($p<0.20$) and sample sizes and numbers of events within these subgroups are sufficient for analysis. Secondary outcomes also will be assessed for heterogeneity of treatment effects. If there is a treatment difference together with evidence of heterogeneity, the relevant covariates and interaction terms will be added to the relevant regression models for formal significance testing. For the primary outcome, we plan for analyses of treatment effects within pre-specified subgroups potentially 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. These analyses will all be considered exploratory.

Data linkages. Necessary identifying data (i.e. Social Security Number, Medicare Beneficiary number) will be obtained from consenting participants to facilitate data linkage to the National Death Index and to Medicare claims for planned analyses of survival data and health care utilization data. Patients who refuse to provide these data will still be eligible to participate in this study with informed consent.

Interim analyses. Because both spinal and general anesthesia are considered standard care for hip fracture surgery, we do not intend to consider early termination on the basis of efficacy data;

however interim efficacy data will be provided to the DSMB to permit benefit-to-risk assessments.

Data management. The Clinical Research Computing Unit of the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics will serve as the REGAIN Data Coordinating Center will provide a central location for data processing and management. All study data will be collected via an online data management system using the Oracle Remote Data Capture software, with encrypted transmission of remotely-entered data. Separate data entry systems and study databases will be maintained for identifiable data required for patient follow-up, and de-identified clinical data; unique study identifiers will be assigned to each patient to allow for linkage across databases. Data will be stored on secure computing servers and will be restricted via password protections to only those individuals who are authorized to work on the trial. Specific privilege assignments within the database will also be employed to limit the types of data that authorized users may access to the minimum required by their role in the trial. Electronic audit trails will be used to capture and record changes to database contents automatically.

Site training

Training for REGAIN sites will be provided via: (1) in-person training meetings, including national kickoff events held in Philadelphia and Chicago in February and October 2016, for orientation to the study protocol and procedures; (2) online webinars for training and certification in the study data management system; and (3) self-learning activities for training and certification in study processes and selected study instruments. As necessary, site personnel may be required to undergo re-training, either through the on-line webinars or during site visits made by Coordinating Center staff.

Prior to initiation of data collection at a given site, all site personnel will be required to submit signed attestations of completion of required training tasks and to demonstrate proficiency in specific key competencies. Where relevant, site personnel will be required to demonstrate proficiency in data entry into the online data management system, with demonstration of competency of both basic data entry and troubleshooting functions. For personnel completing 3D-CAM assessments, demonstration of proficiency will be required via satisfactory completion of assessments for three simulated patients using standardized web videos, with a correct overall diagnosis (delirium present/absent) and correct identification of all 4 features of CAM-defined delirium[41] required for a passing score. For personnel completing data abstraction functions, certification demonstration of proficiency in abstraction of required data into study case report forms from two de-identified intraoperative anesthesia records.

Monitoring

The REGAIN study monitoring plan incorporates remote and on-site monitoring appropriate for the risk level involved in the trial.[42] Remote monitoring will take place via regular communication between Clinical Coordinating Center staff and recruiting site staff via e-mail, conference call and web conference; communications will take place at regular intervals to review progress and identify issues, and as needed to address identified concerns. Sites will be provided with interval performance reports on recruitment progress, consent rates, data completeness, and data timeliness.

Additional remote monitoring activities will include review and re-abstraction of selected chart data from participating sites by trained staff within the Clinical Coordinating Center. Site personnel will de-identify portions of the medical record for the first 3 randomized patients and as needed thereafter and transmit them to the University of Pennsylvania for re-abstraction.

Identified discrepancies will be reported back to site staff for resolution and continuous quality improvement. Additional documents may be requested on an as-needed basis for monitoring purposes. Coordinating center staff will also regularly review the completeness and timeliness of all data entries, and adherence to treatment in each study arm for each site. Non-adherence and data issues will be individually investigated and remediated as necessary.

On-site monitoring at participating sites will take place 1-2 times over the study period for review of the study regulatory binder for completeness and accuracy, review of consent documents, selected patient medical records for data completeness and accuracy, and on-site evaluation of adherence to study processes and procedures.

Data and safety monitoring

All serious adverse events, as well as all non-serious adverse events that are unexpected and judged to be related to the study treatment, will be recorded in the study database and reported as required to local IRBs and to the University of Pennsylvania IRB. Data and safety monitoring will be the responsibility of the Study Director/PI, the study Biostatistician, site Clinical Directors, and an independent Data Safety Monitoring Board (DSMB) selected by the study Principal Investigator.

The DSMB roles, responsibilities, and operating procedures are defined by the REGAIN DSMB Charter. The DSMB will be composed of 5-7 independent, multidisciplinary experts 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 DSMB will not be blinded to subject treatment assignment.

The DSMB met 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 after randomization of the first 100 patients and after randomization of ¼, ½, and ¾ of the total planned randomized sample. The DSMB will serve in an advisory capacity to the principal investigator, and recommendations for protocol modifications or revisions to the informed consent document will be communicated directly to the study PI.

Study risks. The risks associated with this study are low. The risk of a breach of confidentiality is small and all possible efforts have been taken to ensure the security of study data and minimize the risks of accidental disclosure of identifiable data elements. The medical risks for participation in this study do not go beyond those risks typically associated with spinal or general anesthesia as used in routine clinical care. 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 standard of care at the local hospital.

Ethics and dissemination

To date, the REGAIN Trial protocol has been approved by the University of Pennsylvania Perelman School of Medicine IRB and by the IRBs or Research Ethics Boards (REBs) of 23 participating US institutions and 2 Canadian institutions. Of currently approved US sites, 6 have designated the University of Pennsylvania Perelman School of Medicine IRB as the IRB of record for this study. Recruitment began on February 12, 2016 and will continue through the end of 2019.

Protected health information will only be shared with research team members as required for completion of designated study tasks; patient contact information will be transmitted to the Clinical Coordinating Center for follow-up via secure network servers as described above. Electronic data and demographic information will be accessed only as necessary for completion of study follow-up tasks, and will not be printed or transferred from the study server to any secondary media. Lists will be maintained identifying all team members with access to identifiable study data, and dates and times of database access by team members will be logged.

Engagement and dissemination

Patient and stakeholder partners will be involved at all stages of the REGAIN trial. The lead patient partner for REGAIN is the Center for Advocacy for the Rights and Interests of the Elderly (Philadelphia, PA); in addition, the REGAIN trial leadership receives input from a patient partner panel which includes CARIE staff and 7 lay members, including patients, caregivers, and community members. Patient partners reviewed and provided input the study protocol, and will meet at regular intervals over the course of the study to receive updates on study progress and provide ongoing input related to study conduct and interpretation and dissemination of results.

The lead stakeholder partner is the Gerontological Society of America (GSA; Washington, D.C.); in addition, the REGAIN trial leadership will receive input from a stakeholder partner panel which will be convened by GSA staff and will include representatives from relevant national stakeholder organizations. Stakeholder partners will help design and implement dissemination strategies for study findings to relevant lay and professional audiences.

Dissemination plans include presentations at local, national, and international scientific conferences, and publications in scientific and lay journals. Study results will also be presented by study staff to affected populations within communities served by participating trial sites.

CONCLUSIONS

The REGAIN Trial is a multicenter trial that will randomize 1,600 older adults to receive either spinal anesthesia or general anesthesia for hip fracture surgery. Through an innovative pragmatic design and implementation across a broad range of geographic locations, hospital types, and practice settings, REGAIN will yield important new information to directly impact the care and outcomes of the more than 1.6 million patients undergoing surgery for hip fracture each year worldwide.

AUTHORS' CONTRIBUTIONS

MDN, SSE, FES, RF, JSM, and JLC each made substantial contributions to the conception or design of the study protocol. MDN conceived the overall study and wrote the first draft of the protocol and this manuscript. FES, JSM, SSE, and JLC provided critical input regarding the design of the study intervention, study outcomes, and study procedures; MDN, SSE, and RF designed the data analysis and management plan. MDN, SSE, FES, RF, JSM, and JLC revised the protocol critically for important intellectual content and approved the final version to be published. MDN, SSE, FES, RF, JSM, and JLC agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The views, statements, and opinions presented in this work are solely the responsibility of the author(s) and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Competing interests

Drs. Neuman, Ellenberg, and Feng report grants from Patient Centered Outcomes Research Institute, during the conduct of the study. Dr. Neuman reports grants from National Institutes of Health, outside the submitted work. Drs. Magaziner, Carson, and Sieber report grants from University of Pennsylvania subcontract as study investigator, during the conduct of the study. Dr. Magaziner reports personal fees from Novartis, personal fees from Scholar Rock, personal fees from Ammonett LLC, personal fees from Viking, personal fees from Sanofi, outside the submitted work.

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Box 1. Inclusion and exclusion criteria for the REGAIN Trial

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

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 (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.

Box 2. Treatment regimens for the REGAIN trial
Instructions for patients randomized to receive 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.
Instructions for patients randomized to receive 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.

Table 1. Pragmatic design features of the REGAIN trial. Domains are adapted from the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)framework of Thorpe et al (2009). The ten listed domains for the REGAIN trial are described and characterized in relation to design aspects common to pragmatic (effectiveness) vs. explanatory (efficacy) trials.

PRECIS Domain(s)	Assessment
1. Participant eligibility criteria	Since this study will enroll all hip fracture patients without contraindications to regional or general anesthesia across a group of diverse academic and community sites across the US, it is extremely pragmatic in this domain.
2 & 3. Experimental & comparison interventions—flexibility	Treating physicians will receive brief, simple, and highly flexible care protocols for patients randomized to receive spinal anesthesia; these protocols will state explicitly that co-interventions will are permitted based on clinical judgment. The study is maximally pragmatic in this domain.
4 & 5. Experimental & comparison interventions—practitioner expertise	Study protocols will be administered by clinical anesthesia staff without requirements for additional training in specific anesthesia techniques or advanced expertise. The study is maximally pragmatic in this domain.
6. Follow-up intensity	In-hospital outcomes will be assessed by 3 brief assessments over the first 3 post-operative days and by chart review at discharge. Blinding will not be required for in-hospital assessments to maximize study feasibility across a range of hospital settings. Post-discharge follow-up will occur via brief minute phone interviews at 60, 180, and 365 days by assessors who are blinded to treatment assignment. Survival will be assessed by searches of vital records files. The study is highly pragmatic in this domain.
7. Primary trial outcome	The primary outcome (death or inability to walk across a room at 2 months) is simple and pragmatic; secondary outcomes are also pragmatic endpoints, including overall disability, return to pre-fracture residence and all-cause mortality.
8. Participant compliance with prescribed intervention	Randomization to regional vs general anesthesia will be clearly stated in the study consent form. Since patients who do not want either regional or general anesthesia will be unlikely to enroll in the trial, the study is more explanatory than pragmatic in this domain.

Table 1 (continued). Pragmatic design features of the REGAIN trial. Domains are adapted from the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) framework of Thorpe et al (2009). The ten listed domains for the REGAIN trial are described and characterized in relation to design aspects common to pragmatic (effectiveness) vs. explanatory (efficacy) trials.	
9. Practitioner adherence to study protocol	Practitioner adherence to treatment assignment will be monitored and efforts will be made to limit deviations from assigned treatments; the study is more explanatory than pragmatic in this regard.
10. Analysis of primary outcome	All randomized patients will be included in the primary analysis; additional analyses will be adjusted for compliance with the study protocol. A priori subgroups will be examined; the proposal is moderately pragmatic in this regard.

Table 2. Visit schedule for the REGAIN trial

	STUDY PERIOD										
	Pre-allocation	**Allocation**	**Post-allocation**								**Closeout**
TIME POINT[a]	***Pre-operative ($-t_1$)***	***POD 0 (t_0)***	***POD 0 (t_1)***	***POD 1 (t_2)***	***POD 2 (t_3)***	***POD 3 (t_4)***	***POD 30 (t_5)***	***POD 60 +/- 30 (t_6)***	***POD 180 +/- 45 (t_7)***	***POD 365 +/- 60 (t_8)***	***POD 365 +/- 60 (t_9)***
ENROLLMENT											
Eligibility	X										
Informed consent	X										
Allocation		X									
INTERVENTION			X								
ASSESSMENTS											
Medical history	X										
Locomotion ability	X							X	X	X	
Pain scales	X			X	X	X		X	X	X	
Short Blessed Test (cognition)	X					X		X	X	X	
WHODAS 2.0 (disability)	X							X	X	X	

Table 2 (continued). Visit schedule for the REGAIN trial

	STUDY PERIOD										
	Pre-allocation	**Allocation**	**Post-allocation**								**Closeout**
TIME POINT	***Pre-operative*** ***($-t_1$)***	***POD 0 (t_0)***	***POD 0 (t_1)***	***POD 1 (t_2)***	***POD 2 (t_3)***	***POD 3 (t_4)***	***POD 30 (t_5)***	***POD 60 +/- 30 (t_6)***	***POD 180 +/- 45 (t_7)***	***POD 365 +/- 60 (t_8)***	***POD 365 +/- 60 (t_9)***
ASSESSMENTS											
3D-CAM (delirium)	X			X	X	X					
Bauer scale (satisfaction)[b]						X					
Medical record review: intraoperative & postoperative events[c]							X				
Mortality (medical record review/telephone follow up)							X	X	X		
Mortality (National Death Index)										X	
Study Closeout											X

Notes: a. REGAIN uses standard surgical conventions for counting postoperative days. Postoperative day 0 indicates the day of surgery, corresponding to the 24-hour period beginning on midnight of the day that includes the surgery end time. Postoperative day 1 indicates the 24-hour period beginning at the first midnight after the surgery end time. b. For patients discharged prior to postoperative day 3, the Bauer Scale is administered on the day of hospital discharge. c. For patients who are discharged or who die prior to POD 30, medical record abstraction occurs at the time of discharge or death. Medical record abstraction encompasses only the index hospitalization. WHODAS: WHO Disability Assessment Schedule; POD: Postoperative Day; 3D-CAM: 3-minute assessment for CAM (Confusion Assessment Method)-defined delirium.

Appendix: REGAIN Investigator Group

REGAIN Executive Committee:
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Executive Secretary (non-voting): Rosemary Madigan, University of Pennsylvania School of Medicine, Philadelphia PA

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Protocol page	Manuscript page
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**i**	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**i**	**4**
	2b	All items from the World Health Organization Trial Registration Data Set	**2**	**See full protocol**
Protocol version	3	Date and version identifier	**i**	**See full protocol**
Funding	4	Sources and types of financial, material, and other support	**i**	**22**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**i**	**21**
	5b	Name and contact information for the trial sponsor	**i**	**1-2**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**Documented outside protocol**	**22**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**Documented outside protocol**	**Appendix**

Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**3-5**	**6-7**
	6b	Explanation for choice of comparators	**4**	**6**
Objectives	7	Specific objectives or hypotheses	**5-6**	**7**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**6-7**	**7**
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**6**	**7, 12**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**6**	**Box 1**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**10-11**	**Box 2**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**11**	**Box 2**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**12**	**17**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**11-12**	**See full protocol**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**8-10**	**9-10**

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**12-16**	**Table 2**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**17-18**	**10-11**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**6-7**	**11**
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**8**	**12**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**11**	**12**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**11**	**12**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**11-12**	**10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**22-23**	**See full protocol**
Methods: Data collection, management, and analysis				

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**12-16**	**8-10**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**26**	**See full protocol**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**24-26**	**15**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**18-19**	**12-13**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**18-19**	**13-14**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**18-19**	**13-14**
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**23**	**17-18**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**23**	**15**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**27**	**18**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**27**	**15**

Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**27**	**18**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**N/A**	**18**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**28**	**11**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**N/A**	**8**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**24**	**19**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**29**	**23**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**24-26**	**15**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**16**	**See full protocol**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**29**	**19-20**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Documented outside protocol**	**19-20**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**26**	**See full protocol**

Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Appendix**	**See full protocol**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**N/A**	**N/A**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): protocol for a pragmatic, international multicenter trial

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Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): protocol for a pragmatic, international multicenter trial

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ABSTRACT

Introduction: Hip fractures occur 1.6 million times each year worldwide, with substantial associated mortality and losses of independence. At present, anesthesia care for hip fracture surgery varies widely within and between countries, with general anesthesia and spinal anesthesia representing the two most common approaches. Limited randomized evidence exists regarding potential short- or long-term differences in outcomes between patients receiving spinal or general anesthesia for hip fracture surgery.

Methods: The REGAIN Trial (Regional versus General Anesthesia for Promoting Independence after Hip Fracture) is an international, multicenter, pragmatic randomized controlled trial. 1,600 previously ambulatory patients aged 50 and older will be randomly allocated to receive either general or spinal anesthesia for hip fracture surgery. The primary outcome is a composite of death or new inability to walk 10 feet or across a room at 60 days after randomization, which will be assessed via telephone interview by staff who are blinded to treatment assignment. Secondary outcomes will be assessed by in-person assessment and medical record review for in-hospital endpoints (delirium; major inpatient medical complications and mortality; acute postoperative pain; patient satisfaction; length of stay) and by telephone interview for 60-, 180-, and 365-day endpoints (mortality; disability-free survival; chronic pain; return to the pre-fracture residence; need for new assistive devices for ambulation; cognitive impairment).

Ethics and dissemination: The REGAIN trial has been approved by the ethics boards of all participating sites. Recruitment began in February 2016 and will continue until the end of 2019. Dissemination plans include presentations at scientific conferences, scientific publications, stakeholder engagement efforts, and presentation to the public via lay media outlets.

Registration details: The study is registered at clinicaltrials.gov, NCT02507505 (last updated June 20, 2016).

Trial registration number: NCT02507505

STRENGTHS AND LIMITATIONS OF THIS STUDY

- REGAIN will evaluate outcomes of common anesthesia techniques for hip fracture surgery, an event that occurs over 1.6 million times each year world-wide, through an international, multicenter, randomized trial.
- Pragmatic, "real-world" treatment protocols are reflective of current practice and will allow the results to be generalized across a range of care settings.
- Collection of patient-centered outcomes data, including measures of functional independence, at up to 1 year will provide insight into the relationship between the study intervention and meaningful patient endpoints.
- Input by patients and stakeholders at each stage will improve translation and dissemination of eventual results to affected communities.
- Data collection for certain in-hospital adverse events will rely on medical record review; as such, events that are not recorded in the medical record may not be captured.

INTRODUCTION

Over 1.6 million hip fractures occur each year worldwide, with major consequences for the individual and society.[1 2] Within 12 months of fracture, 25% of patients die,[3 4] and half of previously community-dwelling patients either die or require new nursing home admission.[5] Hip fractures create substantial needs for informal caregiving [6 7] and post-acute and long-term care involving major costs to society;[8] the estimated costs attributable to hip fractures in the US exceeded $12 billion in 2005 and will exceed $18 billion by 2025.[9]

Nearly all patients with hip fractures undergo surgical treatment. Anesthesia for hip fracture surgery varies widely in practice,[10 11] with general anesthesia and spinal anesthesia representing the two most common approaches.[12] Available studies comparing outcomes with spinal versus general anesthesia for hip fracture surgery have been reviewed elsewhere.[13-17] While spinal anesthesia has been theorized to improve outcomes by avoiding the need for tracheal intubation and exposure to general anesthetics, available randomized studies have yielded equivocal findings regarding the relative superiority of one technique over the other with regard to either short-term morbidity and mortality or longer-term functional recovery.

Existing randomized studies are characterized by major shortcomings. A 2016 Cochrane review of trials comparing spinal versus general anesthesia for hip fracture surgery between 1977 and 2012 rated the quality of available evidence as “very poor” for all outcomes studied.[13] 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 that the available evidence “is old and does not reflect

current practice."[18] In particular, few data are available to characterize the impact of anesthesia technique on patient-centered outcomes, such as functional recovery or satisfaction.

Study objectives

The REGAIN Trial (Regional versus General Anesthesia for Promoting Independence after Hip Fracture) will evaluate the effect of spinal versus general anesthesia on recovery of ambulation at 60 days after randomization (primary outcome) and other patient-centered outcomes measured at up to one year. Our primary hypothesis is that patients who receive spinal anesthesia will demonstrate improved ambulation at 60 days after randomization compared to patients who receive general anesthesia. The membership of the REGAIN investigator group is described in the Appendix.

METHODS AND ANALYSIS

Study design. We will perform a randomized, multicenter, pragmatic active comparator study of two standard care approaches to anesthesia for hip fracture surgery (i.e. spinal and general anesthesia). 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. The primary outcome will be assessed at 60 days after randomization by a telephone interviewer blinded to treatment assignment. As noted below, all post-discharge outcomes (including the primary endpoint) will be assessed in a blinded fashion; however, to increase the feasibility of trial implementation across sites with varied staffing capabilities, we will encourage but not require those staff that will assess in-hospital endpoints to be blinded to treatment assignment.

Pragmatic design features of the REGAIN trial. The development process for the REGAIN Trial protocol engaged patients, stakeholders, researchers, and clinicians to develop a pragmatic study design that would yield findings with relevance to clinical practice across a range of settings. We used the PRECIS tool[19] to formalize the implications of specific design choices for the nature of the REGAIN trial as a pragmatic (effectiveness) trial versus an explanatory (efficacy) trial (**Table 1**) across a range of domains.

Eligibility criteria appear in **Box 1.**

Baseline assessment. As shown in the study assessment schedule (**Table 2**), enrolled patients will undergo a pre-randomization assessment that includes a medical history questionnaire, a brief medical record review, and selected assessments to assess: (1) pre-fracture disability, as measured by the 12-item World Health Organization Disability Assessment Schedule, version 2.0 (WHODAS 2.0), a validated measure that assesses cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society;[20 21] notably, as we are unable to measure pre-fracture disability prospectively in this population, we will rely on patient recall of pre-fracture self-performance in WHODAS 2.0 domains; (2) cognitive status at the time of interview, as measured by the Short Blessed Test, a well-validated brief cognitive screening tool;[22 23] (3) delirium at the time of interview, as measured by the 3D-CAM a well-validated brief assessment tool with high sensitivity and specificity for delirium;[24 25](4) pre-fracture pain symptoms, as measured by items adapted from the Brief Pain Inventory;[26 27] and (5) resilience at the time of interview, as measured by the Brief Resilience Scale, a short, validated tool measuring an individual's ability to "bounce back" from a stressful event.[28] We will collect contact information for the patient and for alternate contacts as required for telephone follow-up.

In patients who agree to provide these data, social security numbers and Medicare beneficiary identifiers will be collected for relevant database linkages.

Interventions. We will randomly allocate patients to receive standard care spinal anesthesia or standard care general anesthesia. Apart from the decision regarding the primary anesthetic technique (spinal versus general anesthesia), all decisions about pre-operative, intraoperative, and post-operative care will be made by the clinical care team.

The intervention will occur by providing the treating clinical anesthesia staff written instructions (**Box 2**) directing them to perform a standard care spinal anesthetic or a standard care general anesthetic. For patients who are randomized to receive spinal anesthesia, instructions will be provided to titrate any sedation to maintain arousability to tactile stimulus or voice, and to rate the level of sedation in the anesthetic record at least once between induction and emergence on a scale of 1 (deep sedation) to 5 (alert) based on the arousability subscale of the Observer's Assessment of Alertness/Sedation scale.[29]

Outcomes

Primary outcome: Independence in walking at 60 days after randomization. The primary outcome will be assessed by telephone interview at 60 days after randomization. This assessment will be conducted centrally by the study Clinical Coordinating Center at the University of Pennsylvania. Assessments will be conducted by staff who will be blinded to treatment assignment. 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. For patients who are unable to provide their own responses, available secondary informants will be interviewed regarding the participant's ability to walk independently at 60 days.

The primary outcome for REGAIN was selected based on consultation with patient and stakeholder partners as a clinically meaningful measure that also predicts key long-term outcomes. Data from the Baltimore Hip Studies indicate that patients who were unable to walk at 60 days demonstrated high rates of persistent inability to walk at one year (OR 11.1, 95% CI 6.6-18.7), one year mortality (OR 3.6, 95% CI 1.9-6.5), and new nursing home placement at one year (OR 6.2, 95% CI 3.9-9.7) compared to those who could walk independently at 60 days.[30]

Our selection of the primary outcome for REGAIN was also informed by the successful use of the same endpoint in the FOCUS trial, a 2,100 patient randomized trial compared two different transfusion strategies after hip fracture surgery.[30 31] The use of telephone follow-up was chosen based on the past successful use of this approach in prior studies,[31-33] as well as to allow for a high degree of standardization and quality assurance for outcome data collection across a diverse group of institutions, potentially including those with limited access to research staff.

Secondary outcomes (in-hospital): (1) Postoperative delirium will be assessed by study staff prior to randomization and daily from postoperative day 1 through postoperative day 3 or the day of discharge (whichever occurs first) via the 3D-CAM;[24 25] (2) acute postoperative pain will be assessed by study staff via in-person interview daily from postoperative day 1 through postoperative day 3 or the day of discharge (whichever occurs first) via items adapted from the Brief Pain Inventory;[26 27](3) satisfaction with anesthesia care will be assessed on postoperative day 3 or the day of discharge (whichever occurs first) via the Bauer Patient Satisfaction Questionnaire;[34] (4) inpatient mortality and major inpatient morbidity will be assessed via chart review by site staff using standardized outcome definitions following hospital discharge, death, or at 30 days after surgery, whichever occurs first. To increase the feasibility of trial

implementation across diverse sites, we will encourage but not require those staff that will assess in-hospital endpoints to be blinded to treatment assignment.

Secondary outcomes (post-discharge): Secondary outcomes will be collected via telephone interview by blinded study staff at 60, 180, and 365 days after randomization. Secondary outcomes will include: (1) overall health and disability, as assessed via telephone interview with patients or proxies via the WHODAS 2.0;[20 21] (2) chronic pain, as assessed via two adapted Brief Pain Inventory items to assess the extent of pain at worst and on average over the past 7 days. (3) cognitive function, as assessed by the Short Blessed Test;[22 23] (4) independence in locomotion and need for assistive devices for walking (i.e. cane, walker), and (5) location of residence (i.e. home versus nursing facility). Finally, vital status will be assessed via patient and/or proxy telephone interview at approximately 60, 180, and 365 days after randomization and via a National Death Index (NDI) search for US patients in the final year of the study.

Sample size planning

The REGAIN trial will randomize 1,600 patients to spinal versus general anesthesia for hip fracture surgery. Assuming a 34% rate of the primary outcome (death or new inability to walk at 60 days) in the general anesthesia arm (the rate observed in the 2,000-patient FOCUS trial),[33] this sample will provide 80% power to detect a relative risk of 0.78 for the primary outcome among patients receiving spinal versus general anesthesia and 90% power to detect a relative risk of 0.76 at an alpha value of 0.05. Sample size calculations allow for 5% loss to follow-up for the primary outcome and a 5% crossover rate from spinal to general anesthesia based on available published data on rates of spinal anesthetic failures in clinical practice.[35-37]

The planned sample will also provide sufficient power for testing of hypotheses related to secondary outcomes. In terms of overall health and disability, a change of 8 points or greater represents a clinically important difference for the WHODAS 2.0;[20] the WHODAS 2.0 standard deviation among adults aged 75-85 with more than one chronic physical condition is 15.8%.[38] Given these assumptions our sample will provide over 99% power to detect a clinically significant difference in disability at 180 days between groups.

Recruitment

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 for their patients to be enrolled. For potentially eligible patients, a member of the REGAIN research team will approach the patient and/or their legally authorized representative (based on local IRB guidance) between the time of diagnosis and the time of surgery to explain the study, complete a brief screening evaluation, and obtain written informed consent. For patients who are too sick or who are not competent to give their own permission to enter the study, consent will be obtained from the patient's legally authorized representative if permitted by the local IRB.[39]

REGAIN recruiting sites have been selected to represent a broad range of geographic locations and practice settings in the US and Canada, including large teaching and non-teaching hospitals and smaller community facilities. The site selection process for REGAIN included consideration of annual hip fracture volume, presence of buy-in from clinical leaders, research infrastructure, and past experience with randomized trials.

Allocation

Randomization will be carried out on the day of surgery immediately prior to start of anesthesia care and will be performed centrally through an online electronic data management system after confirmation with the assigned anesthesia and orthopedic surgery providers that the patient is suitable for randomization. Site research staff will obtain the randomization assignment from the data management system web portal immediately prior to surgery and will communicate the treatment assignment to the anesthesia team. Participants will be randomly assigned to one of the two treatment regimens in a 1:1 ratio. For each arm, balanced randomization of subjects, stratified by site, sex, and fracture type (intracapsular versus extracapsular), will be achieved by permuted block randomization with variable block sizes.[40 41] Participants will not be blinded to treatment assignment.

Data analysis and management

Both primary and secondary outcomes will be evaluated under the intention-to-treat principle. All hypothesis tests will be performed using a two-sided significance level (Type I error) of $\alpha = 0.05$. Sensitivity analyses using the actual treatment received (rather than assigned) will be performed and compared with the intention-to-treat analysis results; additional sensitivity analyses will assess the potential impact of missing data due to losses to follow-up.

The primary analysis will compare the proportions of patients who can walk independently at 60 days between groups randomized to spinal versus general anesthesia using the Mantel-Haenszel tests, stratified by site, gender, and fracture type. The Mantel-Haenszel odds ratio will be reported. Stratum-specific odds ratios will be generated and tested for homogeneity across strata using the Breslow-Day test.[42] If the result is significant, separate odds ratios for each stratum will be reported.

The ability to walk independently at each time point (60, 180, and 365 days) will be analyzed using multivariable logistic regression models that control for other covariates, including stratification factors (site, gender, and fracture type), and baseline variables that have potential association with the outcome, with particular attention to any such variable that appears imbalanced between treatment groups. Generalized linear mixed models will be used to perform a repeated measures analysis, looking at the ability to walk at 60, 180, and 365 days. We will use residual (or restricted) maximum likelihood methods for parameter estimates and significance testing. A function of time and the covariates mentioned above will be included as fixed effects in the regression.

The analytical approaches specified for the primary outcome will also be used for the binary secondary outcomes, including need for assistive devices for walking, postoperative delirium, mortality, return to the prior residence, occurrence of any major in-hospital complication. Continuous secondary outcomes including WHODAS 2.0 score, pain scale values, cognitive function score, and patient satisfaction scores will be compared between treatment groups using analysis of variance adjusting for the above stratification factors.

Missing Data. We will evaluate the amount, reasons for and patterns of missing data, with a particular attention to the lost-to-follow-up data, in primary and secondary outcomes. Primary and secondary analyses will assume missing values are "at random," relative to other data that we have collected; if the reasons for missing values suggest that the missingness is "nonignorable" (i.e. not at random), we will develop models for missingness (for example, a selection model where the risk for drop-out depends on some clinical response) and use these models to help us assess the potential impact of missing data on our results.[43 44] We will also do a

"worst case scenario" sensitivity analysis, i.e., all missing 60-day values in one treatment group will be replaced with the worst outcome and those in the other group with the best outcome.

Heterogeneity of treatment effects. Subgroup comparisons will be conducted if any treatment-covariate interactions are at least suggestive ($p<0.20$) and sample sizes and numbers of events within these subgroups are sufficient for analysis. Secondary outcomes also will be assessed for heterogeneity of treatment effects. If there is a treatment difference together with evidence of heterogeneity, the relevant covariates and interaction terms will be added to the relevant regression models for formal significance testing. For the primary outcome, we plan for analyses of treatment effects within pre-specified subgroups potentially 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. These analyses will all be considered exploratory.

Data linkages. Necessary identifying data (i.e. Social Security Number, Medicare Beneficiary number) will be obtained from consenting participants to facilitate data linkage to the National Death Index and to Medicare claims for planned analyses of survival data and health care utilization data. Patients who do not provide these data will still be eligible to participate in this study with informed consent.

Interim analyses. Because both spinal and general anesthesia are considered standard care for hip fracture surgery, we do not intend to consider early termination on the basis of efficacy data; however interim efficacy data will be provided to the DSMB to permit benefit-to-risk assessments.

Data management. The Clinical Research Computing Unit of the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics will serve as the REGAIN Data Coordinating Center will provide a central location for data processing and management. All study data will be collected via an online data management system using the Oracle Remote Data Capture software, with encrypted transmission of remotely-entered data. Separate data entry systems and study databases will be maintained for identifiable data required for patient follow-up, and de-identified clinical data; unique study identifiers will be assigned to each patient to allow for linkage across databases. Data will be stored on secure computing servers and will be restricted via password protections to only those individuals who are authorized to work on the trial. Specific privilege assignments within the database will also be employed to limit the types of data that authorized users may access to the minimum required by their role in the trial. Electronic audit trails will be used to capture and record changes to database contents automatically.

Site training

Training for REGAIN sites will be provided via: (1) in-person training meetings, including national kickoff events held in Philadelphia and Chicago in February and October 2016, for orientation to the study protocol and procedures; (2) online webinars for training and certification in the study data management system; and (3) self-learning activities for training and certification in study processes and selected study instruments. As necessary, site personnel may be required to undergo re-training, either through the on-line webinars or during site visits made by Coordinating Center staff.

Prior to initiation of data collection at a given site, all site personnel will be required to submit signed attestations of completion of required training tasks and to demonstrate proficiency in

specific key competencies. Where relevant, site personnel will be required to demonstrate proficiency in data entry into the online data management system, with demonstration of competency of both basic data entry and troubleshooting functions. For personnel completing 3D-CAM assessments, demonstration of proficiency will be required via satisfactory completion of assessments for three simulated patients using standardized web videos, with a correct overall diagnosis (delirium present/absent) and correct identification of all 4 features of CAM-defined delirium[45] required for a passing score. For personnel completing data abstraction functions, certification demonstration of proficiency in abstraction of required data into study case report forms from two de-identified intraoperative anesthesia records.

Monitoring

The REGAIN study monitoring plan incorporates remote and on-site monitoring appropriate for the risk level involved in the trial.[46] Remote monitoring will take place via regular communication between Clinical Coordinating Center staff and recruiting site staff via e-mail, conference call and web conference; communications will take place at regular intervals to review progress and identify issues, and as needed to address identified concerns. Sites will be provided with interval performance reports on recruitment progress, consent rates, data completeness, and data timeliness.

Additional remote monitoring activities will include review and re-abstraction of selected chart data from participating sites by trained staff within the Clinical Coordinating Center. Site personnel will de-identify portions of the medical record for the first 3 randomized patients and as needed thereafter and transmit them to the University of Pennsylvania for re-abstraction. Identified discrepancies will be reported back to site staff for resolution and continuous quality improvement. Additional documents may be requested on an as-needed basis for monitoring

purposes. Coordinating center staff will also regularly review the completeness and timeliness of all data entries, and adherence to treatment in each study arm for each site. Non-adherence and data issues will be individually investigated and remediated as necessary.

The REGAIN study monitoring and quality assurance procedures will aim to ensure adherence to the assigned treatment for all patients and avoid cross-overs to comparator treatments. Remotely collected data will be reviewed on an ongoing basis to identify crossover events; reasons for individual crossovers are investigated, and sites will be required to file protocol deviation reports where appropriate. The importance of avoiding crossovers will be stressed to site staff on a regular basis in monthly phone-calls and all-investigator e-mails, and sites will be regularly counseled on the need for adherence to aspects of the protocol designed to limit crossovers. Prior to randomization, site personnel will be required to verify that the treating anesthesiologist believes the patient is suitable for randomization and agrees deliver the assigned study treatment; further, site personnel will be encouraged to randomize the patient immediately prior to surgery in order to limit the possibility of crossovers occurring due to changes in clinical status over time or related to changes in anesthesia staffing.

Additional on-site or remote monitoring at participating sites will take place 1-2 times over the study period for review of the study regulatory binder for completeness and accuracy, review of consent documents, selected patient medical records for data completeness and accuracy, and on-site evaluation of adherence to study processes and procedures.

Data and safety monitoring

All serious adverse events, as well as all non-serious adverse events that are unexpected and judged to be related to the study treatment, will be recorded in the study database and reported as required to local IRBs and to the University of Pennsylvania IRB. Data and safety monitoring will be the responsibility of the Study Director/PI, the study Biostatistician, site Clinical Directors, and an independent Data Safety Monitoring Board (DSMB) selected by the study Principal Investigator.

The DSMB roles, responsibilities, and operating procedures are defined by the REGAIN DSMB Charter. The DSMB will be composed of 5-7 independent, multidisciplinary experts 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 DSMB will not be blinded to subject treatment assignment.

The DSMB met 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 after randomization of the first 100 patients and after randomization of ¼, ½, and ¾ of the total planned randomized sample. The DSMB will serve in an advisory capacity to the principal investigator, and recommendations for protocol modifications or revisions to the informed consent document will be communicated directly to the study PI.

Study risks. The risks associated with this study are low. The risk of a breach of confidentiality is small and all possible efforts have been taken to ensure the security of study data and minimize

the risks of accidental disclosure of identifiable data elements. The medical risks for participation in this study do not go beyond those risks typically associated with spinal or general anesthesia as used in routine clinical care. 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 standard of care at the local hospital.

Ethics and dissemination

To date, the REGAIN Trial protocol has been approved by the University of Pennsylvania Perelman School of Medicine IRB and by the IRBs or Research Ethics Boards (REBs) of 26 participating US institutions and 2 Canadian institutions. Of currently approved US sites, 7 have designated the University of Pennsylvania Perelman School of Medicine IRB as the IRB of record for this study. Recruitment began on February 12, 2016 and will continue through the end of 2019, with a target date for submission of the primary trial manuscript of September 30, 2020. Protected health information will only be shared with research team members as required for completion of designated study tasks; patient contact information will be transmitted to the Clinical Coordinating Center for follow-up via secure network servers as described above. Electronic data and demographic information will be accessed only as necessary for completion of study follow-up tasks, and will not be printed or transferred from the study server to any secondary media. Lists will be maintained identifying all team members with access to identifiable study data, and dates and times of database access by team members will be logged.

Engagement and dissemination

Patient and stakeholder partners will be involved at all stages of the REGAIN trial. The lead patient partner for REGAIN is the Center for Advocacy for the Rights and Interests of the

Elderly (Philadelphia, PA); in addition, the REGAIN trial leadership receives input from a patient partner panel which includes CARIE staff and 7 lay members, including patients, caregivers, and community members. Patient partners reviewed and provided input the study protocol, and will meet at regular intervals over the course of the study to receive updates on study progress and provide ongoing input related to study conduct and interpretation and dissemination of results.

The lead stakeholder partner is the Gerontological Society of America (GSA; Washington, D.C.); in addition, the REGAIN trial leadership will receive input from a stakeholder partner panel which will be convened by GSA staff and will include representatives from relevant national stakeholder organizations. Stakeholder partners will help design and implement dissemination strategies for study findings to relevant lay and professional audiences.

Dissemination plans include presentations at local, national, and international scientific conferences, and publications in scientific and lay journals. Study results will also be presented by study staff to affected populations within communities served by participating trial sites.

CONCLUSIONS

The REGAIN Trial is a multicenter trial that will randomize 1,600 older adults to receive either spinal anesthesia or general anesthesia for hip fracture surgery. Through an innovative pragmatic design and implementation across a broad range of geographic locations, hospital types, and practice settings, REGAIN will yield important new information to directly impact the care and outcomes of the more than 1.6 million patients undergoing surgery for hip fracture each year worldwide.

AUTHORS' CONTRIBUTIONS

MDN, SSE, FES, RF, JSM, and JLC each made substantial contributions to the conception or design of the study protocol. MDN conceived the overall study and wrote the first draft of the protocol and this manuscript. FES, JSM, SSE, and JLC provided critical input regarding the design of the study intervention, study outcomes, and study procedures; MDN, SSE, and RF designed the data analysis and management plan. MDN, SSE, FES, RF, JSM, and JLC revised the protocol critically for important intellectual content and approved the final version to be published. MDN, SSE, FES, RF, JSM, and JLC agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The views, statements, and opinions presented in this work are solely the responsibility of the author(s) and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Competing interests

Drs. Neuman, Ellenberg, and Feng report grants from Patient Centered Outcomes Research Institute, during the conduct of the study. Dr. Neuman reports grants from National Institutes of Health, outside the submitted work. Drs. Magaziner, Carson, and Sieber report grants from University of Pennsylvania subcontract as study investigator, during the conduct of the study. Dr. Magaziner reports personal fees from Novartis, personal fees from Scholar Rock, personal fees from Ammonett LLC, personal fees from Viking, personal fees from Sanofi, outside the submitted work.

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Box 1. Inclusion and exclusion criteria for the REGAIN Trial

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

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 (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.

Box 2. Treatment regimens for the REGAIN trial
Instructions for patients randomized to receive 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.
Instructions for patients randomized to receive 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.

Table 1. Pragmatic design features of the REGAIN trial. Domains are adapted from the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)framework of Thorpe et al (2009). The ten listed domains for the REGAIN trial are described and characterized in relation to design aspects common to pragmatic (effectiveness) vs. explanatory (efficacy) trials.	
PRECIS Domain(s)	**Assessment**
1. Participant eligibility criteria	Ghis study will enroll a broad group of hip fracture patients without contraindications to regional or general anesthesia who were ambulatory prior to fracture. Patients will be enrolled from a group of diverse academic and community sites. While the results may not be generalizable to some groups of patients, such as those who were not ambulatory before fracture, the broad eligibility criteria make the study highly pragmatic in this domain.
2 & 3. Experimental & comparison interventions—flexibility	Treating physicians will receive brief, simple, and highly flexible care protocols for patients randomized to receive spinal anesthesia; these protocols will state explicitly that co-interventions will are permitted based on clinical judgment. The study is maximally pragmatic in this domain.
4 & 5. Experimental & comparison interventions—practitioner expertise	Study protocols will be administered by clinical anesthesia staff without requirements for additional training in specific anesthesia techniques or advanced expertise. The study is maximally pragmatic in this domain.
6. Follow-up intensity	In-hospital outcomes will be assessed by 3 brief assessments over the first 3 post-operative days and by chart review at discharge. Blinding will not be required for in-hospital assessments to maximize study feasibility across a range of hospital settings. Post-discharge follow-up will occur via brief minute phone interviews at 60, 180, and 365 days by assessors who are blinded to treatment assignment. Survival will be assessed by searches of vital records files. The study is highly pragmatic in this domain.
7. Primary trial outcome	The primary outcome (death or inability to walk across a room at 2 months) is simple and pragmatic; secondary outcomes are also pragmatic endpoints, including overall disability, return to pre-fracture residence and all-cause mortality.
8. Participant compliance with prescribed intervention	Randomization to regional vs general anesthesia will be clearly stated in the study consent form. Since patients who do not want either regional or general anesthesia will be unlikely to enroll in the trial, the study is more explanatory than pragmatic in this domain.

Table 1 (continued). Pragmatic design features of the REGAIN trial. Domains are adapted from the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) framework of Thorpe et al (2009). The ten listed domains for the REGAIN trial are described and characterized in relation to design aspects common to pragmatic (effectiveness) vs. explanatory (efficacy) trials.	
9. Practitioner adherence to study protocol	Practitioner adherence to treatment assignment will be monitored and efforts will be made to limit deviations from assigned treatments; the study is more explanatory than pragmatic in this regard.
10. Analysis of primary outcome	All randomized patients will be included in the primary analysis; additional analyses will be adjusted for compliance with the study protocol. A priori subgroups will be examined; the proposal is moderately pragmatic in this regard.

Table 2. Visit schedule for the REGAIN trial

	STUDY PERIOD										
	Pre-allocation	**Allocation**	**Post-allocation**								**Closeout**
TIME POINT[a]	***Pre-operative ($-t_1$)***	***POD 0 (t_0)***	***POD 0 (t_1)***	***POD 1 (t_2)***	***POD 2 (t_3)***	***POD 3 (t_4)***	***POD 30 (t_5)***	***POD 60 +/- 30 (t_6)***	***POD 180 +/- 45 (t_7)***	***POD 365 +/- 60 (t_8)***	***POD 365 +/- 60 (t_9)***
ENROLLMENT											
Eligibility	X										
Informed consent	X										
Allocation		X									
INTERVENTION			X								
ASSESSMENTS											
Medical history	X										
Locomotion ability	X							X	X	X	
Pain scales	X			X	X	X		X	X	X	
Short Blessed Test (cognition)	X					X		X	X	X	
WHODAS 2.0 (disability)	X							X	X	X	

Table 2 (continued). Visit schedule for the REGAIN trial

	STUDY PERIOD										
	Pre-allocation	**Allocation**	**Post-allocation**								**Closeout**
TIME POINT	***Pre-operative*** ***($-t_1$)***	***POD 0 (t_0)***	***POD 0 (t_1)***	***POD 1 (t_2)***	***POD 2 (t_3)***	***POD 3 (t_4)***	***POD 30 (t_5)***	***POD 60 +/- 30 (t_6)***	***POD 180 +/- 45 (t_7)***	***POD 365 +/- 60 (t_8)***	***POD 365 +/- 60 (t_9)***
ASSESSMENTS											
3D-CAM (delirium)	X			X	X	X					
Bauer scale (satisfaction)[b]						X					
Medical record review: intraoperative & postoperative events[c]							X				
Mortality (medical record review/telephone follow up)							X	X	X		
Mortality (National Death Index)										X	
Study Closeout											X

Notes: a. REGAIN uses standard surgical conventions for counting postoperative days. Postoperative day 0 indicates the day of surgery, corresponding to the 24-hour period beginning on midnight of the day that includes the surgery end time. Postoperative day 1 indicates the 24-hour period beginning at the first midnight after the surgery end time. b. For patients discharged prior to postoperative day 3, the Bauer Scale is administered on the day of hospital discharge. c. For patients who are discharged or who die prior to POD 30, medical record abstraction occurs at the time of discharge or death. Medical record abstraction encompasses only the index hospitalization. WHODAS: WHO Disability Assessment Schedule; POD: Postoperative Day; 3D-CAM: 3-minute assessment for CAM (Confusion Assessment Method)-defined delirium.

Appendix: REGAIN Investigator Group

REGAIN Executive Committee:
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Jeffrey L. Carson, MD, Rutgers-Robert Wood Johnson Medical School
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Executive Secretary (non-voting): Rosemary Madigan, University of Pennsylvania School of Medicine, Philadelphia PA

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Protocol page	Manuscript page
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**i**	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**i**	**4**
	2b	All items from the World Health Organization Trial Registration Data Set	**2**	**See full protocol**
Protocol version	3	Date and version identifier	**i**	**See full protocol**
Funding	4	Sources and types of financial, material, and other support	**i**	**22**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**i**	**21**
	5b	Name and contact information for the trial sponsor	**i**	**1-2**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**Documented outside protocol**	**22**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**Documented outside protocol**	**Appendix**

Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**3-5**	**6-7**
	6b	Explanation for choice of comparators	**4**	**6**
Objectives	7	Specific objectives or hypotheses	**5-6**	**7**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**6-7**	**7**
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**6**	**7, 12**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**6**	**Box 1**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**10-11**	**Box 2**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**11**	**Box 2**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**12**	**17**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**11-12**	**See full protocol**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**8-10**	**9-10**

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**12-16**	**Table 2**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**17-18**	**10-11**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**6-7**	**11**
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**8**	**12**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**11**	**12**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**11**	**12**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**11-12**	**10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**22-23**	**See full protocol**
Methods: Data collection, management, and analysis				

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**12-16**	**8-10**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**26**	**See full protocol**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**24-26**	**15**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**18-19**	**12-13**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**18-19**	**13-14**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**18-19**	**13-14**
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**23**	**17-18**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**23**	**15**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**27**	**18**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**27**	**15**

Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**27**	**18**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**N/A**	**18**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**28**	**11**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**N/A**	**8**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**24**	**19**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**29**	**23**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**24-26**	**15**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**16**	**See full protocol**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**29**	**19-20**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Documented outside protocol**	**19-20**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**26**	**See full protocol**

Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Appendix**	**See full protocol**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**N/A**	**N/A**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.