PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	Successful Aging after Elective Surgery (SAGES)
Principal Investigator	Sharon K. Inouye, MD, MPH

B1. PURPOSE OF PROTOCOL

Delirium, or acute confusional state, represents a common, serious, and potentially preventable problem for hospitalized older persons. Previous studies have estimated the impact of delirium as over $7 billion per year (2004 U.S. dollars) for hospitalization-related costs and over $100 billion per year for post-hospital costs including institutionalization (*Inouye 2006 NEJM, US DHHS 2004, Leslie 2008*). Despite its clinical and health policy implications, delirium remains poorly examined, and its long-term prognosis remains poorly understood. This Program Project, entitled, **"**Successful Aging after Elective Surgery (SAGES)" seeks, broadly, to conduct a large-scale epidemiologic investigation of delirium and to examine the contribution of delirium to long-term cognitive and functional decline. Understanding novel risk factors [including biomarkers, neuroimaging and reserve markers] and long-term consequences of delirium will be critical to advancing the field, and to developing optimal preventive and treatment strategies. This series of projects will allow us to initiate a discovery process that will enable us to determine whether delirium itself leads to long-term cognitive and functional sequelae and to explore in whom delirium leads to such sequelae. We proposed 4 research projects and 3 cores for our Program Project application, as described below. All of the project leaders are recognized experts in the fields of their proposals. The proposal will center around a prospective cohort of 550 older surgical patients utilized by all projects, as well as 120 non-surgical comparison patients utilized by Projects 1 and 4. In addition, we will conduct Project 5 to facilitate the renewal application for this study. We will conduct a feasibility interview with 100 participants recruited from among currently active participants of the SAGES study. We will also conduct Project 6 with up to 30 SAGES participants to obtain fresh blood specimens to further our understanding of biological basis of accelerated age-related frailty by analyzing metabolomics and inflammatory markers and developing iPS cell lines (~5 per participant). We will only approach SAGES participants who previously indicated their willingness to be approached for other projects.

Project 1--Long-Term Outcomes of Delirium, Leader: Sharon Inouye, M.D.: This study will test the hypothesis that delirium will be independently associated with a higher rate of long-term cognitive and functional decline. We will utilize appropriate epidemiologic and statistical approaches to evaluate the impact of delirium on cognitive functioning in our prospective cohort over time, as reflected by our composite summary neuropsychological measure, as well as long-term functional decline and health care utilization. Importantly, these analyses will control for relevant covariables, including age, gender, education, cognitive reserve indicators, APOE-ε4 status, comorbidity, baseline cognitive impairment, and vascular risk factors, on which detailed information will be collected for this study. A sub-study of project 1 will look at the clinical outcomes of delirium, specifically rates of conversion to mild cognitive impairment (MCI) or dementia, among those who demonstrate significant cognitive decline during the study. A validation-study of project 1 will validate phone neuropsych testing with face-to face neuropsych testing The phone version of the neuropsych testing may be used in the future for patients who are not available for face-to-face interviews. Another sub-study to Project 1 will identify markers of under- and over treated pain and associated adverse outcomes including delirium and prolonged length of stay during the index hospitalization using existing SAGES data and chart review methods to collect additional data.

Project 2--Biomarker Discovery for Delirium, Leader: Edward Marcantonio, M.D.: The goal of this study is to utilize state-of-the-art methods toward the discovery of plasma biomarkers for delirium. Plasma biomarkers will be assessed at 4 time points for this study: baseline, immediately post-operative, hospital day 2, and one-month follow-up. The Luminex multiplex analyzer system will be used to describe a cytokine "signature" associated with delirium. Mass spectrometry proteomics will be used to describe a plasma protein "signature" for delirium. We will also examine the relationship of the cytokine and protein signatures

with long-term cognitive and functional outcomes following delirium. Finally, we will create a repository of plasma and genetic material, which will be used for future biomarker discovery and validation studies for delirium and other surgical outcomes.

Project 3--Neuroimaging of Delirium, Leader: David Alsop, Ph.D.: This study will include 3 sub-studies using magnetic resonance imaging (MRI) to characterize the functional and structural effects of delirium. In the first sub-study, multiple MRI measures, including blood flow, volumetric, and white matter damage measures, will be used to characterize the brains of 150 patients drawn from our prospective cohort, and to determine whether imaging markers can predict the risk of delirium. The second sub-study will examine all enrolled patient 12 months after the index hospitalization (or delirium episode) to identify delirium-specific risk factors and to determine the location and extent of long-term cognitive changes potentially associated with delirium. The third aim will relate imaging findings to measures derived from the other 3 projects.

Project 4--The Role of Reserve in Delirium, Leader: Richard Jones, Sc.D.: This study will utilize the entire cohort, as well as neuropsychological, biomarker, and neuroimaging data from Projects 1-3 to describe a comprehensive, multifaceted model for reserve. Reserve, the resilience of the brain to withstand neuropathological damage, has been extensively evaluated in dementia, but its role in delirium has remained unexplored. The goal is to develop an index for reserve, then to test whether higher reserve is independently associated with a lower rate of incident delirium and less long-term cognitive and functional decline.

Project 5-- SAGES Extension Study, Leaders: Sharon Inouye: This study will collect data for the renewal application of the SAGES study. We will conduct a feasibility interview (n=100). We will recruit current SAGES participants to respond to a questionnaire regarding willingness to participate in additional studies, including a study collecting cerebral spinal fluid samples (CSF) by lumbar puncture (LP); phlebotomy to obtain blood samples; electroencephalogram (EEG); and non-invasive **t**ranscranial magnetic stimulation **(**TMS**)**.

Project 6—SAGES Harvard Initiative on Aging Pilot: Exploring Molecular Mechanisms of Functional Status: This study will involve up to 30 SAGES participants. Each of these participants will be approached and consented specifically for this sub-study, and will provide a fresh blood sample. From the blood sample, up to five Induced Pluripotent Stem Cell (iPSC) lines per participant will be developed in a standardized way to explore differences between the frail and non-frail samples, in order to elucidate potential molecular mechanisms associated with frailty

Core A--Administrative Core, Leader: Sharon Inouye, M.D.: This core will provide the leadership and organization to ensure scientific coordination and integration, and to optimize productivity of all projects and cores. This core will be responsible for overseeing all administrative functions and committees, providing scientific oversight and advisory board meetings, assuring the safety of human subjects and safety monitoring, directing overall grants management including fiscal and timeline adherence, and conducting all reporting activities. This core will directly interface with all projects.

Core B--Epidemiology Core, Leader: Edward Marcantonio, M.D.: This core will recruit a prospective cohort of 550 participants aged 70 years and older from surgical services who will undergo baseline assessments prior to hospitalization or surgery, and who will be followed daily during hospitalization and for 18month-12 years after hospitalization with telephone and face-to-face interviews. This core will be responsible for the screening, recruitment, informed consent, tracking, retention, and follow-up of this cohort, which will be utilized by all projects. An additional 120 non-surgical matched patients will be enrolled from the BIDMC to determine patterns in normal aging, and as a comparison group for Projects 1 and 4.

Core C--Data Management and Statistical Analysis Core, Leader: Richard Jones, Sc.D.: For this core, Dr. Jones will serve as leader and will oversee day-to-day operations. This core will provide data management, statistical analysis and consulting to the other Cores and Projects. The primary responsibilities of this core will be to generate information systems and software for enrolling and tracking participants, receiving and processing of data, generation of data sets, and performing statistical analyses tied to the specific aims of the projects. This core will serve all projects.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Delirium is a common and serious clinical problem. Delirium, defined as an acute decline of cognition and attention, represents a common and serious problem for older persons, particularly in the face of acute illness and hospitalization (*Inouye 1999 AJM, Gleason 2003, Cole 2004*). In general hospital populations, delirium occurs in 14-56% and subsequent hospital mortality rates range from 25-33% (*Inouye 1999 AJM, Gleason 2003, Cole 2004*). In surgical populations, delirium occurs in 15-53% of older patients postoperatively *(Inouye 2006 NEJM)*. The development of delirium in older persons is associated with increased morbidity, functional decline, increased nursing time per patient, higher hospital costs, increased length of hospital stay, higher rates of institutionalization and mortality (*Cole 1993, Inouye 1998 JGIM*). Delirium often initiates a cascade of events culminating in functional decline, caregiver burden, increased morbidity and mortality, and higher health care costs (*Cole 1993, Inouye 1998, Francis 1992, Levkoff 1992, Murray 1993, O'Keefe 1997*). Delirium in older hospitalized patients has assumed particular importance because patients aged ≥ 65 years currently account for more than 48% of all days of hospital care (*AoA 1995*). Based on our earlier work (*Inouye 1999 NEJM, Inouye 1999 AJM*) and extrapolations from Medicare data (*US Dept HHS 2002*), we estimate that each year delirium complicates hospital stays for 20% of the 11.8 million persons age ≥ 65 years hospitalized each year, with an increased hospital cost of $2,500 per patient attributable to delirium. This accounts for over $7 billion (2004 US dollars) of Medicare hospital expenditures attributable to delirium (*Inouye 2006 NEJM*). Additional costs of over $100 billion per year accrue after hospital discharge because of the increased need for nursing home care, rehabilitation services, formal home health care, and informal caregiving costs (*Leslie 2008*). These figures highlight the magnitude of the problem of delirium for older persons.

Delirium may be associated with long-term cognitive impairment and dementia. Previous studies demonstrate that delirium persists much longer than previously believed, with symptoms commonly lasting months to years in some patients (*Levkoff 1992, Rockwood 1993, Levkoff 1994, Marcantonio 2000, Cole 2003, McCusker 2003*). The entities of persistent delirium (*Levkoff 1992, Rockwood 1993, Levkoff 1994, Marcantonio 2000, Cole 2003, McCusker 2003*) and reversible dementia (*Clarfield 1988*) blur the boundaries between these conditions. Some epidemiologic studies have documented an increased risk for long-term cognitive decline in patients with delirium, even after controlling for relevant covariables in some studies (See Table 1); however these prior studies have been contradictory and limited by high attrition rates, infrequent follow-up, inclusion of dementia patients, lack of baseline pre-delirium assessment, lack of follow-up neuropsychological testing, and incomplete control for confounders and competing causes of cognitive decline. Some causes of delirium, such as hypoxia or hypoglycemia, may lead to neuronal death and permanent cognitive sequelae (*Inouye 1997*). In addition, neuroimaging studies demonstrate regions of hypoperfusion in patients with delirium (*Yokota 2003, Fong 2006*), suggesting that delirium may incite a derangement in brain vascular function that may lead to dementia in some cases. Finally, delirium may herald the onset of dementia in many cases. This phenomenon is well-recognized clinically, where clinicians and family members report that some patients "never return to baseline" after developing delirium. While the underlying causes do contribute to the poor prognosis associated with delirium, current evidence suggests that the development of delirium may independently contribute to these poor outcomes. Given that delirious patients (with associated agitation and lethargy) are at increased risk for aspiration, pressure ulcers, pulmonary emboli, and decreased oral intake, the finding that delirium is associated with worsened outcomes even after controlling for baseline patient characteristics and etiologic factors is not surprising. Thus, delirium may identify patients at high risk for poor outcomes, and may also independently contribute to poor outcomes.

Delirium may be associated with long-term functional decline. Delirium has been independently associated with long-term functional decline in at least 6 previous studies with follow-up periods ranging from 1 month to 12 months, including hip fracture (*Dolan 2000, Marcantonio 2000, Olofsson 2005*), medical (*McCusker 2001, Andrew 2005*), and long-term care (*Kiely 2006*) populations. Not all of these studies were able to fully control for important confounders. Moreover, some of these studies revealed an association of delirium with functional outcomes only for basic physical functioning and not for the more cognitively-based instrumental activities of daily living (*McCusker 2001*), and others showed effects for shorter-term follow-up periods (e.g., 1 month) and not for longer-term periods (e.g., 6 months)(*Marcantonio 2000*). Another 4 studies did not show any significant

impact of delirium on long-term functional outcomes at 3 months to two years follow-up, including hip fracture (*Furlaneto 2007, Zakriya 2004*), medical (*Vida 2006*), and long-term care (*Katz 2001*) populations. Thus, the contribution of delirium to long-term functional decline warrants further examination. Previous studies have not examined the inter-relationship of cognitive and functional outcomes, which is an innovative exploratory aim for Project 1

In addition, Project 6 will further the understanding of the biological basis of accelerated age-related frailty and decline in functional status.

TABLE 1. Studies on cognitive outcomes of delirium

Reference	Population	N Attrition	FU	Cognitive Outcomes Associated with Delirium	Predelirium Cognitive Testing	FU Neuro-psych Testing	Control for Confoun-ders
Monk 2008	Non-cardiac surgery patients age 70+ without dementia	1064 (13%)	7 days 3 mos	Delirium associated with POCD at 7 days only	Yes	Yes	Yes
Cole 2008	Older medical inpatients	361 (53%)	2,6,12 mos	Delirium *not* associated with MMSE/IADL decline, NH, death	No	No	Yes
Bickel 2008	Hip surgery patients, age 60+	200 (17%)	8, 38 mos	Delirium associated with cognitive impairment and NH	No	No	Yes
Kat 2008	Elderly hip surgery patients	112 (56%)	Once 2-3 yrs	Increased risk of cognitive disorders (eg, dementia, MCI)	No	No	No
Fann 2007	Patients post-myeloablative hematopoietic stem cell transplantation (age 20-62)	90 (34%)	80 days	Significantly worse executive functioning, attention, and processing speed	Yes	Yes	Yes
Wacker 2006	Elderly hip or knee replacement, nondemented	90 (68%)	2 yrs	Worse cognitive function and increased risk of dementia	No	Yes	No
Lundstrom 2003	Elderly hip fracture patients, nondemented	100 (32%)	5 yrs	6-fold increased risk of new dementia diagnosis	No	No	Yes
McCusker 2001	Elderly emergency department patients	315 (38%)	1 yr	Lower MMSE scores at one year (vs. controls)	No	No	Yes
Rahkonen 2001	Community-dwellers, age 85+	366 (46%)	3 yrs	Increased risk for new diagnosis of dementia	No	No	No
Katz 2001	Nursing home and assisted living	102 (6%)	1 yr	Greater cognitive decline by neuropsychological testing	No	Yes	Yes
Rahkonen 2000	Elderly community dwellers hospitalized for delirium	51 (22%)	2 yrs	Increased risk for new dementia	No	No	No
Dolan 2000	Hip fracture patients	674 (55%)	2 yrs	Worsened MMSE at 2 yrs	No	No	Yes
Rockwood 1999	Hospitalized elderly medical patients	203 (8%)	2.7 yrs	3-fold increased risk of incident dementia	No	No	Partial
Francis 1992	Hospitalized elderly medical patients	223 (8%)	2 yrs	Lower MMSE scores at follow-up (vs. controls)	No	No	Yes
Koponen 1989	Psychogeriatric unit	70 (53%)	1 yr	Cognitive deterioration at 1 yr	No	No	No

FU=follow-up; Neuropsych=neuropsychological testing; mos=months, yrs=years; POCD=postoperative cognitive dysfunction; MMSE=Mini-Mental State Examination; IADL=instrumental activities of daily living; NH=nursing home; MCI=mild cognitive impairment

Delirium may be preventable. A major motivator for this study is that delirium, and thus its effects on long-term outcomes, may be preventable. In fact, recent studies have provided strong evidence that a substantial proportion of delirium episodes may be preventable. Our clinical trial (*Inouye 1999 NEJM*), which applied a multicomponent intervention targeted towards 6 delirium risk factors, demonstrated a reduction in incident delirium from 15.0% in the usual care group to 9.9% in the intervention group (matched odds ratio=0.60, 95% confidence interval 0.39-0.92), with a significant reduction in the total number of days with delirium and episodes of delirium in the intervention group. In a randomized trial of proactive geriatric consultation for reducing delirium after hip fracture, Marcantonio et al (*Marcantonio 2001*) demonstrated a

reduction in delirium from 50% in the usual care group to 32% in the intervention group (relative risk=0.64, 95% confidence interval 0.37-0.98), with a greater reduction in cases of severe delirium. In a study of 374 older adults admitted to a tertiary care hospital, Naughton et al (*Naughton 2005*) found that delirium prevalence rates fell from 40.9% to 19.1% ($p<0.001$) following the implementation of a multifactorial intervention to reduce delirium. Tabet and colleagues (*Tabet 2005*) demonstrated that an educational intervention for medical and nursing staff reduced the point prevalence of delirium among hospitalized older patients from 19.5% in a control ward to 9.8% in the intervention ward ($p<0.05$). Taken together, these recent studies provide strong evidence that at least 30-40% of delirium cases may be preventable in hospitalized older persons.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

A.1. Brief overview of the study*:*

Four projects are proposed addressing several interlocked hypotheses, and exploring: the long-term cognitive and functional outcomes of delirium (Project 1); plasma biomarkers for delirium and long-term decline (Project 2); neuroimaging markers for delirium and long-term decline (Project 3); and the role of cognitive and brain reserve in delirium and long-term decline (Project 4). All projects involve a prospective cohort of 550 older patients scheduled for major surgery who are free of dementia, and who will be enrolled in the community prior to surgery and followed prospectively initially for 18- 72 months and then extended to 12 years from their initial hospitalization with serial evaluations for neuropsychological and functional outcomes. Below, we will first describe the methods common to all 4 projects, followed by a description of relevant methods pertinent to individual studies involving biomarkers and neuroimaging.

A.2. Overall study design:

We proposed a 7 year prospective observational study which got extended to 12 years, including 6 months for initiation, 30 months for patient enrollment, 42 months (additional) to complete all patient follow-ups, and 6 months for statistical analyses and manuscript preparation. The proposed study will enroll 550 elective non-cardiac surgical patients, each of whom will be followed prospectively for a minimum of 18 months and up to 72 months initially and then extended to 12 years, after their initial hospitalization. All patients will undergo a baseline evaluation prior to hospitalization, including neuropsychological and frailty testing. The primary outcomes for this project are cognitive decline, based on a neuropsychological test battery, and functional decline. When admitted for the index hospitalization, patients will be assessed daily for the development of delirium, the major predictor variable. Subsequently, each patient will be followed prospectively for a minimum of 18 months or until death or termination of the project period with a face-to-face interview at 1 and 2 months, telephone interviews at 4, 9, 15, 21 and 27 months and face-to-face interviews including neuropsychological testing every 6 months up ~~t~~o 12 years. Medical records for each patient from all hospitalizations (including outside hospitals) will be reviewed at the end of their index hospitalization, after each subsequent hospitalization, after their final study **interview or end** of data collection (12 years)--to identify any hospitalizations (including recurrent delirium and repeat surgeries), intercurrent illnesses, new diagnoses, unidentified hospitalizations, or unreported deaths.

We will also examine a non-surgical comparison group, which will be at low risk for hospitalization, and will be matched with the surgical group. Other than surgery, they will meet all other inclusion and exclusion criteria for the surgical group. The purpose of the group is to help us evaluate the cognitive trajectory in the absence of hospitalization, surgery, and delirium and to quantify retest (learning) effects. For this group, we will enroll 120 primary care patients from BIDMC, who will be frequency matched (using a prospective frequency matching algorithm) to the surgical group on age, gender, education, baseline cognitive function, and comorbidities (i.e., both vascular and nonvascular comorbidities). We have successfully implemented this type of prospective matching in our pilot work and previous studies (*Charpentier 2001*).

For Project 5, we will enroll current SAGES patients (n=100). Interim analysis of data collected from the current SAGES study has identified a need for additional biomarkers and other neurophysiologic measures to complement and further the work done thus far in SAGES. With this feasibility study we want to evaluate if SAGES participants would be willing to undergo additional procedures.

Project 6: For this project, the Fried frailty index (*Fried 2000*) will be utilized to identify contrasting aging phenotypes (frail and robust/non-frail) in the SAGES I original sample. 1. We will enroll current SAGES I participants (up to n=30) to identify 15 frail and 15 robust/non-frail individuals, and to obtain fresh blood specimens to develop iPS cell lines (5 per participant). 2. We will utilize the iPS cell lines

to probe various molecular-physiologic differences between the frail and non-frail samples in 4 different labs:

a) Neurophysiology: The Yankner lab will differentiate the iPS cells into neurons and probe neurophysiologic differences
b) Muscle function: The Wagers lab will differentiate the iPS cells into muscle cells and probe physiologic differences at the molecular level
c) Mitochondrial function: The Haigis lab will explore differences in mitochondrial functioning, applying metabolomic and other molecular approaches
d) Nicotinamide adenine dinucleotide (NAD) function: The Sinclair lab will explore differences in oxidative functioning particularly in relationship to NAD functioning.

3. We will develop and validate a human platform to further examine frailty in vitro in future larger studies
4. The Lieberman (BIDMC) lab will run the Walston inflammatory index, which is known to be correlated with the Fried frailty index. This will allow us to validate that the frailty phenotype for this study has been correctly identified in our chosen samples.

A.3. <u>Setting and Subjects</u>: The surgical cohort will be enrolled from 2 sites, the Beth Israel Deaconess Medical Center (BIDMC) and Brigham and Women's Hospital (BWH). The BIDMC is a 601-bed Harvard-affiliated acute-care teaching hospital with over 40,000 admissions, 750,000 outpatient visits, and 10,000 surgeries each year. The BWH is a 747 bed Harvard-affiliated acute-care teaching hospital with over 45,000 admissions, 754,000 outpatient visits, and 30,000 surgeries each year. Both hospitals serve large community and referral populations. The surgical patients will be identified from the operating room advanced booking schedule and will be approached and enrolled (after permission from their surgeons) in either the subject's choice of their home or during an office visit. From our pilot studies, we anticipate that 473 surgical patients per year will meet our eligibility criteria across the 2 sites and will be available for the study, yielding a eligible:enroll ratio of 2.4:1; we require 200 subjects per year. Thus, we anticipate that we will have adequate availability of patients to conduct the study. The comparison patients will be enrolled from two primary care clinics at the BIDMC, Health Care Associates (HCA) and Senior Health (SH). Together, these clinics serve a population of about 5,000 patients age ≥ 70 years per year, with 4,000 per year at HCA and 1,000 per year at SH. To maximize comparability of the comparison and surgical groups, the two groups will be frequency-matched on age, gender, education, baseline cognitive function, and comorbidities. The details of subject selection will be provided in Section C below.

A.3.1. <u>Study Procedures</u>: The study procedures, including screening, baseline, hospital, and follow-up assessments are detailed below. All face-to-face assessments will be conducted either in the subject's place of residence or in the out-patient clinics, according to the convenience and preference of the subject. Our previous studies and pilot work support our ability to accomplish the proposed study procedures. Drs. Inouye and Marcantonio have conducted previous studies that have utilized all the proposed methods. Moreover, we will put into place back-up methods, such as revisits, tailoring time and procedures, and follow-ups by the study investigators themselves to assure completion of all steps. In Dr. Inouye's previous study of over 919 frail medical patients (*Inouye 1999 NEJM*), complete follow-up at 12 months was available in 81% of subjects, with 17% lost due to mortality and only 2% true losses to follow-up. The feasibility interviews will be conducted over the phone.

A.3.1.1. <u>Research staff</u>: All research staff, comprised of research nurses and experienced clinical research interviewers, will undergo intensive training, following standardized procedures, in all questionnaires and research methods. They will be carefully trained to handle emergency issues in the home setting, and the project and core leaders will be available to provide back-up at all times. Baseline standardization and inter-rater reliability assessments will be conducted to verify consistency of all staff on the primary outcomes (including the neuropsychological test battery and functional outcomes), as well as key risk factor variables (including the delirium assessment). Interviewer quality checks with inter-rater reliability assessments on all key study variables will be performed every 6 months for the duration of the study.

A.3.1.2. Screening assessment: The purpose of the screening assessment is to verify subject eligibility. Based on a 10-minute patient interview along with medical record review, information will be collected to establish eligibility criteria and to rule out the presence of delirium at baseline [Modified Mini-Mental State Examination (3MS), digit span, Confusion Assessment Method (CAM), Memorial Delirium Assessment Scale (MDAS) and Delirium Symptom Interview (DSI) (*Simon 2006*)]. The screening will also complete the first stage of our two-stage process to exclude patients with dementia. All screening information will be entered into a tablet computer by the interviewer, and immediate subject eligibility will be determined based on internal algorithms to determine all inclusion and exclusion criteria, to rule out delirium and first-stage dementia, and to verify meeting frequency-matching criteria for enrollment among comparison subjects. This real-time enrollment procedure using the tablet computer has been pilot tested, and verified to be usable, efficient, and acceptable to subjects and staff.

A.3.1.3. Baseline assessment interviews: The purposes of the baseline assessment are to describe the subjects, to document baseline neurocognitive function, to characterize baseline risk factors for delirium and cognitive decline, and to measure potentially confounding factors. This assessment will be conducted immediately following the screening assessment in eligible patients. The 80-minute baseline interview will collect information on cognitive functioning (neuropsychological test battery), demographics, education, occupation, medical diagnoses, comorbidity, medications, health habits (e.g., smoking, alcohol), hearing, mobility, basic and instrumental activities of daily living, depression, and anxiety. In a pilot study, we have verified that these interviews are feasible and tolerable in older persons. A family or caregiver interview will be conducted to establish the subject's baseline cognitive functioning, to assess for evidence of dementia [DQ *(Silverman 1987)*], and to determine any recent changes in mental status. Based on our previous and pilot studies, about 3-4% of participants will not have a family member or caregiver available to participate in these interviews; in these cases, we will approach (with the patient's consent) friends, neighbors, visiting nurses, or other reporters about the patient's baseline functioning. All enrollment and baseline assessments will be completed prior to the scheduled surgical admission.

A.3.1.4. Hospital assessments: The purpose of the hospital assessment is to monitor daily for development of delirium and to assess precipitating factors. We anticipate that all patients in the surgical group will be hospitalized. Automatic systems will be in place to notify the principal investigator immediately whenever an enrolled study patient is admitted to the BIDMC or BWH. Upon admission, the patient will be seen by the study team in the hospital, and will undergo daily 10-15 minute interviews including a cognitive screen, digit span test, CAM, DSI, and MDAS ratings. Precipitating factors (e.g., infections, immobilization, surgical procedures, post-surgical complications) will be assessed by interview and review of the medical record using standardized, validated methods applied in our previous studies. The initial hospitalization during the study period will be considered the index hospitalization (admission will be zero-time), and the timing of follow-up will begin from this time. For study purposes readmission within 24 hours is considered a continuation of the hospital stay. Our study team is highly experienced in conducting such interviews in hospitalized persons, which will assist in assuring retention, as well as avoiding any interference with ongoing medical care.

A.3.1.5. Post-hospitalization follow-up assessments: Several types of follow-up assessments will be conducted, as detailed below. These are all timed in relationship to zero-time, which is admission to the index hospitalization. Intercurrent illnesses and re-hospitalizations will be assessed at each follow-up time-point. If patients are hospitalized at the time of a scheduled follow-up assessment, we will wait for one month from hospital discharge to complete the follow-up assessment, to minimize the effects of acute illness on cognitive functioning. A detailed tracking system to track all participants over time will be developed. Some attrition is anticipated at each follow-up time point (due to mortality and losses to follow-up in this older population), as detailed in Core B. These attrition rates are accounted for in all power calculations below.

A.3.1.5.1. Face-to-face interview or phone interviews at two weeks (Delirium group only): The purpose of this 10-15 minute face-to-face or phone interview is to repeat the delirium assessment to better assess the duration and persistence of the index delirium episode. This interview will be conducted at 2 weeks after hospital admission in patients who had delirium at any time during the index hospitalization. This interview will be conducted in all settings of care, including

hospital, home, assisted living, post-acute, or nursing home settings. We have extensive experience conducting interviews in all these settings, and the initial informed consent process will include these follow-up interviews. The two-week time period was selected for this interview, because previous work by our group has demonstrated the prognostic importance of the two week period: patients who resolve their delirium by 2 weeks regained their baseline functioning, whereas those with persistent delirium did not (*Kiely 2006*).

A.3.1.5.2. Retest face-to-face interviews at one and two months follow-up (Retest 1 and 2): The purpose of these 45 minute face-to-face interviews is to repeat our delirium assessments and neuro-psychological test battery to test for both the persistence of delirium and to evaluate retest (learning) effects. All subjects will be interviewed, although only a subset will have developed delirium while hospitalized. The Retest 1 interview (at 1 month) will assess for immediate learning or retest effects, particularly in the patients with normal cognitive functioning. The Retest 2 interview (at 2 months) will assess for delayed learning effects, which our preliminary results suggest are likely to be present in the delirious patients. Patients will also be asked about any rehospitalizations or intercurrent illnesses.

A.3.1.5.3. Telephone follow-up interviews (4, 9, 15, 21 and 27): The purpose of these 10-15 minute telephone interviews is to assess delirium status, functional status, intercurrent illnesses, rehospitalizations, or death. These interim telephone interviews are considered essential to maximize retention, and to conduct brief cognitive testing, discover unreported hospitalizations, and track deaths. This interview will include a validated telephone version of the MMSE (*Roccaforte 1992*), which we have used in previous studies, telephone version of the CAM (*Marcantonio 1998, JGIM*), ADLs/IADLs, recording of intercurrent illnesses, and dates and locations of hospitalizations.

A.3.1.5.4. Face-to-face follow-up interviews (6, 12, 18, then every 6 months up to 12 years): The major purpose of these 45 minute interviews is to obtain comprehensive neuropsychological and functional measures to rate our primary outcomes. These interviews will include the neuropsychological test battery, as well as the 3MS, digit span test, CAM, DSI, and MDAS ratings, ADLs, IADLs, SF36, Montreal Cognitive Assessment (MoCA), falls, sleep disturbance, smoking, alcohol, living situation, hearing and vision tests, intercurrent illnesses, and information on re-hospitalization, institutionalization, and death. If the subject is hospitalized at the time of the scheduled follow-up, then this interview will be postponed until one month after hospitalization to minimize the effects of the acute illness/hospitalization on the neuropsychological testing results. At each of these follow-up interviews, a surrogate will also be interviewed to complete the DQ, and proxy ratings of delirium and functional status (ADL, IADL) either face-to-face or by telephone.

A.3.1.5.5. Medical record, health care utilization and vital status reviews (after index hospitalization, each hospitalization after the index hospitalization, and after final interview): Medical records will be obtained from the index hospitalization, and later from all subsequent hospitalizations, and reviewed for information on development of delirium, intercurrent illnesses, new diagnoses, new surgical procedures, and deaths. Information on hospitalizations is obtained at each of the follow up interviews (telephone and face-to- face). We anticipate that patients may be hospitalized at a large number of different hospitals from which we plan to request medical records. Our informed consent process will include permission to obtain these outside medical records. A standardized medical record abstraction form has already been developed to systematically collect this information. Based on our previous work, these abstractions will take approximately 60 minutes per hospitalization. Development of delirium will be assessed using our chart review method, which has been previously validated (*Inouye 2005*). The final medical record review will be conducted after the patients have their final study interview (18month -12 years).

We will also obtain a HIPAA waiver to for acquisition of Medicare data from the Research Data Assistance Center (RESDAC) and data about the vital status of participants from the National Death Index (NDI). Medicare and NDI data is essential for our study, and will be utilized by Project 1 to assess the association of delirium and health care utilization, health outcomes and death. We fulfill all 4 requirements needed to waive the informed consent to obtain Medicare and NDI data:

a. The research involves no more than minimal risk to the subjects. We will only compare health care utilization data with hospital data and will only publish aggregated data without identifiers. We will use

the same approach as described under B.5.2. Any identifiers will be kept in a password-protected data file, accessible only by trained, HIPAA-certified research staff. The data file will be stored on a password-protected server, and will not be stored on any portable media. All study results will be presented only as statistical aggregates that will neither identify nor permit identification of individual participants.
b. The waiver or alteration will not adversely affect the rights and welfare of the subjects. Data analysis will be performed to produce summary statistics. The right sand welfare of the subjects will never be adversely affected.
c. The research could not practicably be carried out without the waiver or alteration since many of ours subjects are no longer in the study, due to death, moved out of our catchment area, or were lost to follow-up and
d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation. We regularly send a newsletter to participants with general updates and if available, results of our research.

A.3.1.5.6. Procedures for the comparison group: The comparison group will undergo the same screening and baseline interviews, surrogate interview at baseline, and follow up interviews with neuropsychological testing and functional assessment at 0,1,2,12,18, 36months up to 12 years. Entry into the study (zero-time) for this group will be the date of the baseline interview.

A.3.2. Study Variables.

A.3.2.1. Study Variables and Co-Variables: **Table 2** indicates the major study variables to be used for the proposed project, categorized according to the source of information, timing of assessment collecting the information, and purpose or use in the proposed analyses.

A.3.2.2. Major Predictor Variables: Major predictor variables to be explored in our analyses will include delirium variables (presence, severity, duration).

A.3.2.3. Delirium variables: Delirium will be assessed prospectively as our major predictor variable. Delirium presence, severity, duration, and recurrence will be determined, as detailed below.

A.3.2.3.1. Delirium presence: The presence of delirium will be rated by the dichotomous yes/no) diagnosis of delirium based on the validated Confusion Assessment Method (CAM) algorithm. This 4-item algorithm will be used to make a diagnosis of delirium based on DSM criteria. It has excellent psychometric properties, and is widely used in both research and clinical settings. The CAM rating will be completed at baseline, daily during each hospitalization, and at each follow-up assessment, based on information from the interview, 3MS (baseline/every 6 mos) or other cognitive screen (daily in hospital), digit span testing, DSI, and MDAS. Delirium by interviewer rating (CAM criteria) will be augmented with delirium rated as present by medical record review during the index hospitalization, since delirium can occur between interviews. For this study, we are assuming a delirium rate of at least 25% for the surgical cohort. We are also assuming that the vast majority of delirium occurs (or at least begins) in the hospital setting; delirium is rare in community settings. The Delirium Symptom Interview (*Albert 1992*) will be used to rate delirium symptoms and is useful to help with the completion of the CAM rating. This is a brief instrument that includes both questions asked directly of the patient and a series of structured observations. It is used specifically to determine the presence or absence of eight key features of delirium, as originally defined by the DSM-III criteria. Use of this method in conjunction with the CAM has been previously described (*Simon 2006*). For hospitalizations during follow-up, a validated chart rating of delirium (*Inouye 2005*) will be completed.

A.3.2.3.2. Delirium severity: Delirium severity will be rated with the widely-used Memorial Delirium Assessment Scale (*Breitbart 1997*), a 10-item scale that uses information from the MMSE and structured observations to rate delirium severity. Each item is rated as 0-3, to generate a 0-30 scale (30=most severe).

A.3.2.3.3. Delirium duration and recurrence: Delirium duration will be determined as the total number of delirium-days (as rated by a positive CAM rating) during hospitalization in the

study period; this variable will include only days of delirium by direct delirium assessments. Daily delirium ratings will occur only during hospitalization. To better assess the duration of the index delirium episodes, we will also conduct a face-to-face or phone interview with the patient at 2 weeks after hospital admission in patients who had delirium during the index hospitalization. Delirium recurrence will be determined as the total number of delirium episodes, which must be separated in time by at least 48 hours. Delirium recurrence can be counted for any delirium episode, including those determined by direct interviews, telephone or chart review. Recurrent and persistent delirium will be handled as time-varying covariates in secondary analyses.

A.3.3. Outcome Measures:

A.3.3.1.. Summary Measure of Neuropsychological Test Battery, General Cognitive Performance (GCP): A battery consisting of a number widely used neuropsychological measures of cognitive functions thought to be sensitive to cognitive decline will be administered to surgical patients at baseline and at 1,2, 6, 12, and 18-month follow up, and every 6 months thereafter up to 12 years months. These measures were chosen either because they have appeared in the literature as valid measures for the detection of cognitive decline, or because they have been employed in our own previous work for this purpose. In addition to assessing the cognitive domains relevant to our study, all measures have excellent norms covering the range of expected demographic characteristics of our sample, and as a battery are expected to be sensitive and specific across a wide range of premorbid abilities with minimal ceiling and floor effects. Whenever possible, tests were selected that had alternate forms or when these were not available were felt not to be subject to large or unpredictable practice effects. A nearly identical battery was used in our preliminary study, where the battery was well-tolerated on repeated administration in elderly surgical patients, and was demonstrated to have minimal ceiling or floor effects and to be responsive to change over time. Note also that this battery represents the consensus of 3 of our consultants with longstanding clinical and research experience in the cognitive assessment of older adults (Drs. William Milberg, neuropsychologist; Eran Metzger and Gary Gottlieb, geriatric psychiatrists). Based on this revised neuropsychological battery, we have created a new summary measure, General Cognitive Performance (GCP).

A.3.3.2. Functional outcomes, health care utilization and vital status: We will assess ADLs, IADLs, and SF36 (physical functioning domain) at baseline, 6, 12, 18 months, and every 6 months thereafter up until 12 years. Evaluation of Katz's ADLs (*Katz 1963*) assesses the ability to perform 7 basic care skills (feeding, bathing, grooming, using the toilet, transferring, and walking), with each activity scored from 0 (unable) to 1 (with help) to 2 (without help). The scale is scored from 0 to 14, with lower scores indicating functional impairment. The Instrumental Activities of Daily Living scale, IADLs (*Lawton 1969*) assesses the ability to perform 7 complex activities (using the telephone, grocery shopping, using transportation, cooking, housekeeping, taking medications, and handling finances), scored similarly to ADLs and yielding a score from 0 to 14, with lower scores indicating functional impairment. We will assess leisure activities with the short version of the Minnesota Leisure Time Physical Activities Questionnaire (*Pereira 1997*). The Minnesota Leisure Time Physical Activities Questionnaire assesses frequency and average duration 7 common activities. We will assess grip strength with a handgrip dynamometer and walking speed with a timed 3.5 metered walk (*Fried 2000*). (The SF-36 (*Ware 1992*) is a multi-purpose, short-form health survey, which may be the most widely used generic health outcome measure worldwide, used in over 4000 published articles to date (*Garratt 2002, Turner-Bowker 2002*). The SF-36 includes 36 items which aggregate into 8 domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and 2 summary measures (physical and mental health. We will examine each functional measure separately (ADL, IADL, and SF-36 physical functioning domain). We will also create a composite functional measure based on the ADL and IADL, using Rasch scaling to score a latent composite *(Rasch 1960*) as done in our previous studies.We will also assess health care utilization and by analyzing Medicare data as well as vital status by analyzing the National Death Index..

A.4. Procedures specific to Project 2 (Biomarkers):

A.4.1. Blood acquisition: In collaboration with the **Epidemiology Core**, we will collect blood from all 550 surgical cohort participants at 4 time points: 1) at the time of the baseline study assessment

(baseline), 2) immediately after surgery in the post-anesthesia care unit (PACU), 3) on postoperative day 2 (POD 2), and 4) one-month after surgery. We will also collect a single baseline blood sample on 120 participants in a non-surgical comparison group. During the baseline assessment, three green top tubes (30 cc) will be collected. At all follow-up time points, two green top tubes (20 cc) will be collected. Blood samples will be collected via peripheral venipuncture or central venous line (if available in the PACU and on POD 2). Blood samples will be collected into sterile vacuum tubes using either a vacutainer or butterfly system, at the preference of the phlebotomist. Every attempt will be made to "piggyback" our blood collection on clinically scheduled blood draws. For participants being assessed at home, blood will be drawn by a trained member of our research team. All collected blood with be centrifuged to separate plasma from cellular products, divided into small samples, and frozen at -80C for future use.

A.4.2. Biomarker discovery methods

Using these samples, at the end of year 2 we will create a matched longitudinal biomarker discovery sample of 50 surgical participants with delirium and 50 matched surgical participants without delirium. In year 4 of our study we will create an independent biomarker validation sample of 100 surgical participants (50 with delirium and 50 matched controls without delirium). Using the biomarker discovery sample, we will describe a cytokine "signature" for delirium using the Luminex multiplex analyzer system that simultaneously measures 28 plasma cytokines. We will confirm this cytokine signature in the discovery sample and validate it in the biomarker validation sample using Enzyme – linked Immunosorbant Assays (ELISA). Similarly, using the biomarker discovery sample, we will use quantitative mass spectrometry proteomics to describe a plasma protein "signature" for delirium. We will perform two validations: first, using proteomics in the biomarker validation sample, and then using ELISA in the combined discovery and validation samples. Using the combined biomarker discovery and validation samples, we will examine the relationship of the cytokine and protein signatures for delirium with cognitive and functional outcomes up to 18 months after non-cardiac surgery.

A.4.3. Measurement of the Apo E allele

Using genetic material obtained from the baseline blood samples, we will perform Apo-E genotyping for all participants to be used as a covariable in analyses examining long term cognitive decline.

A.4.4. Creation of a biorepository

Using all blood samples from our surgical and non-surgical participants, we will create a bio-repository of genetic material and plasma, a resource for future biomarker discovery studies. The banked specimens will be labeled only with a study number and stored in a -80C freezer at BIDMC. A list linking study numbers to participants will be kept in a secure computer database. In the future, the frozen plasma or DNA may be shared with other scientists after a formal application procedure and scientific review. Only samples will be shared of participants who agreed to it. All such studies will be carried out under the close supervision of the study team. In these cases, the study investigators will maintain confidentiality of the specimens and provide no identifying information to the other scientists. We plan to store these specimens indefinitely. None of the results from these studies will be shared with participants or their family members, and none will become part of the medical record.

A.5. Procedures specific to Project 3 (Neuroimaging):

A.5.1. Subject Selection:

To increase the rate of delirium in the imaging study to an anticipated 40%, we will select 150 patients from the larger sample based on a combination of resource availability and randomization
Participants in the neuroimaging study must also be free from the following MRI contraindications: pacemaker; MRI incompatible metal implant; recently implanted vascular clip (less than 1 month); history of claustrophobia; metal fragment within the eye; or other contraindication to MRI based on standard clinical screening criteria. Note: titanium total joint replacements and metal implants in bone are not contraindications to MRI. Should a subject indicate they may have had an injury of metal to the eye, an orbital x-ray exam is required. A radiologist will review the exam and will decide if it is safe for the subject to participate.

A.5.2. MRI

All imaging will be performed on one of our whole body scanners located on the East Campus of the Beth Israel Deaconess Medical Center. This study will be using a 3.0 Tesla scanner that has dedicated time for research related imaging.

A.5.3. Scanning Procedure

Prior to scanning, subjects must complete an MRI screening form designed to identify any MR contraindications. Subjects will lie on the scanner table. The coil, or antenna, will be placed around the patient's head. The coil is a hard plastic box frame, open on all sides with space to slide the patient's head inside. Ear plugs will be provided to the subject and a pneumatic squeeze ball that triggers an alert at the scanner console when squeezed will be provided. The patient will be able to communicate with the MRI technologists at all times during the exam.

Subjects will be instructed to remain still and breathe normally. The MRI will acquire data about the structure and function of the brain, using advanced imaging techniques including 3D MPRAGE anatomical imaging, FLAIR T2 weighted imaging, standard T2 imaging, diffusion tensor imaging, and arterial spin labeling (ASL) perfusion imaging. No contrast agents will be administered for this study. Two-way intercoms will be used to monitor the comfort of the patients during the 45 minute examination.

A.5.4 Incidental Findings

In the event of an incidental finding a specifically designed MRI Safety Protocol will be followed to ensure standardized handling of incidental findings. This MRI Safety protocol has the purpose of providing clinical backup to MRI research staff for any unexpected medical issues that arise in the course of participants undergoing MRI scans and to manage incidental findings on MRI, including maintenance of a database of such findings. If a suspicious finding is observed by the study staff, the finding will be reported to the study PI, the MRI on-call research physician, and to the MRI Research Medical Officer. If the finding is confirmed as suspicious and requiring a follow up, the PI or an MD coinvestigator will contact the patient and explain the recommendation for a full clinical imaging evaluation. The investigator will communicate the recommendation to the surgeon and primary care provider with a medical explanation of the finding. All incidental findings are reported to the SAGES safety officer, Dr. Jeff Silverstein. The SAGES MRI Safety Panel will maintain a list of all incidental findings and all MRI incidental findings will be included in the annual progress reports.

A.6. Procedures specific to Project 1 Sub-study (Clinical outcomes of delirium):

A.6.1 Subject Selection: study subjects at follow-up evaluations (i.e., 6-, 12-, and every 6-months thereafter) who: (1) have a complaint of cognitive change, verified by a proxy (IQCODE test); (2) decline in HVLT total recall to ≤ 25.5; (3) are classified by the clinical consensus panel at the quarterly review as MCI or dementia; or 4) are recommended at the discretion of the consensus panel for further evaluation because the history or cognitive performance is atypical, or consensus could not be reached, will be eligible for this sub-study. Once identified, study subjects will be contacted by phone and the purpose and details of the sub-study explained. If the subject agrees to participate, a separate informed consent will be signed. A randomly selected group of subjects without cognitive change will also be evaluated as controls, and will follow the same procedures.

A.6.2 Clinical Examination: This will include a clinical history, neurologic examination, targeted blood tests (thyroid function, vitamin B12, and liver function tests) and neuroimaging (non-contrast clinical brain MRI or head CT). This evaluation meets standards for routine clinical care of patients with cognitive complaints. In addition, a clinical dementia rating (CDR) score, delayed paragraph recall, and Hachinski score will also be obtained. It is anticipated that such an evaluation would take no more than 45 to 60 minutes to complete, with blood work requiring less than 6 ml of blood, and a non-contrast clinical MRI or Head CT requiring between 30 and 60 minutes to obtain. Using the data

from the clinical examination, a diagnosis of normal, MCI-- including classification as early or late MCI as defined in the ADNI-GO trial (Petersen 2010) --or dementia will be made following the revised 2011 Alzheimer's Association-NIA criteria (McKhann 2011). An informant who knows the patient well will be interviewed by phone or in-person on the day of the clinical examination.

A.6.3 Disclosure of Results: Although specific diagnoses will not be disclosed to study subjects, with the subject's consent, the results will be shared with their primary care physician, who would manage ongoing clinical care, or recommend referral to a clinical neurologist (with disclosure, as appropriate). The neuroimaging study (brain MRI or head CT) will be interpreted by a clinical neuro-radiologist and included in the medical record.

A.7. Procedures specific to Project 1 Validation- Study:

A.7.1 Subject Selection: Study participants who completed a face-to face neuropsych battery within the last two weeks will be contacted by phone and the purpose and details of the validation-study explained. If the subject agrees to participate, a verbal consent will be obtained over the phone.

A.7.2 Instruments: This validation study will include previously approved neuropsych battery of the main SAGES study (HVLT-R, short cognitive screen (S-COG), Digit Span, Verbal and Category Fluency) and in addition, the Boston Naming Test –Short Form for phone administration and D-KEFS verbal fluency test. It is anticipated that the testing will take no more than 20 -30 minutes to complete.

A.7.3 Outcomes: Results of the phone testing will be validated against the test performed during the face-to face neuropsych testing that is being done every 6 month for the main study. The validation study will reveal if the results of neuropsych test administered over the phone are comparable to face-to-face testing.

A.8. Procedures specific to the Project 1 Pain – Delirium Study

A.8.1 Subject Selection: All surgical patients will be included.

A.7.2 Instruments: This sub-study will use data that has already been collected (demographic data, hospital interview data, chart abstraction) and will also collect additional data from the medical charts of the index hospitalization including detailed medication information and evidence of under-treated (e.g., changes in pain medication dose/type/frequency, patient pain rating, family of medical staff comments) and over-treated pain (e.g., patient lethargy, family and staff comments, reduced dose of pain medication).

A.7.3 Outcomes: This sub-study will identify markers of over- and under -treated pain and the association of these markers with delirium and increased length of stay.

TABLE 2. DESCRIPTION OF STUDY VARIABLES

Variable/Instrument	Source of Information	Purpose
Patient and General Descriptors:		
Demographics	INT, MR	Descriptive; Covariable/confounder
Education/Occupation	INT	Descriptive; Covariable/confounder
Surgical type	MR	Descriptive; Covariable
Cognitive function:		
• Neuropsychological test battery	INT	Primary outcome
• 3MS (*Teng 1987*)	INT	Screening variable and used to rate delirium
• Digit span test (*Cummings 1985*)	INT	Used to rate delirium
• Delirium:		
-CAM (*Inouye 1990*)	INT	Major predictor variable (SA1)
-MDAS--delirium severity (*Breitbart 1997*)	INT	Major predictor variable (SA2)
-DSI—delirium symptoms (*Albert 1992*)	INT	Major predictor variable (SA2)
-Delirium duration/persistence	INT	Major predictor variable (SA2); secondary outcome
-Delirium recurrence	INT	Major predictor variable (SA2)
• Premorbid intelligence, WTAR (*Wechsler 2001*)	INT	Covariable/confounder
• Cognitive reserve* (See also Project 4 proposal)	INT	Covariable/confounder
• Telephone MMSE (*Roccaforte 1992*)	INT	Used to rate delirium
• DQ *(Silverman 1987***)**	FAM	Descriptive; used to rate dementia
• APOE –Є4 allele	LAB	Covariable/confounder
Physical function:		
• ADL (*Katz 1963*)	INT/FAM	Primary outcome
• IADL (*Lawton 1969*)	INT/FAM	Primary outcome
• SF36 (physical functioning domain) (*Ware 1992*)	INT	Primary outcome
• Activities (*Cornoni-Huntley 1986*)	INT/FAM	Covariable
• Minnesota Leisure time test (Taylor 1978)	INT	Covariable
• Timed walk and grip strength	INT	Covariable
Other delirium risk factors:		
• Anesthesia type and duration	MR	Covariable
• Specific Activities Scale (SAS) Class	INT; MR	Covariable
• Abnormal labs (Na, K, Glu, Hct)	MR	Covariable
• Vision impairment, Jaeger test (*Runge 2000*)	INT	Covariable
• Hearing impairment, Whisper test (*MacPhee 1988*)	INT	Covariable
• BUN/Cr ratio ≥ 18 *(Inouye 1993*)	MR, LAB	Covariable
• Precipitating factors *(Inouye 1996*)	INT, MR	Covariable
• Intercurrent illnesses (*Inouye 1996*)	INT, MR	Covariable
• Intra- and post-operative complications	MR	Covariable
• Poor nutrition (Body Mass Index, weight loss, Alb)	INT;MR	Covariable
• Brief Pain Inventory (*Cleeland 1989*)	INT	Covariable
Illness- related factors:		
• Medical diagnoses	MR	Covariable
• APACHE II score (*Knaus 1985*)	MR	Covariable
• Charlson comorbidity score (*Charlson 1987*)	MR	Covariable/confounder
• Medications	INT, MR	Covariable
• Health habits (alcohol, smoking)	INT, MR	Covariable
• Vascular risk factors (smoking, HTN, DM, chol, VD)	INT, MR	Covariable/confounder
• Formal delirium interventions	MR	Covariable
• Hospital (index) LOS	RN INT, MR	Covariable
• Repeat surgeries, re-hospitalizations, recurrent delirium	INT	Covariable
• Inter-current Illness (Katz 1996)		
Affect:		
• Depression (GDS-short form) (*Sheikh 1986*)	INT	Covariable
• Anxiety (Beck Anxiety Inventory) (*Beck 1990*)	INT	Covariable
Other secondary outcomes:		
• Dementia diagnoses (clinician's consensus diagnosis)	INT, FAM, MR	Secondary outcome
• SF-36 general health and well-being *(Ware 1992*)	INT	Secondary outcome
• Rehospitalization(s)	INT, FAM, MR	Secondary outcome
• Institutionalization	INT, FAM, MR	Secondary outcome
• Death, Cause of death	FAM, MR, NDI	Secondary outcome; censoring variable

*Cognitive reserve markers include: education, occupation, income, wealth, head circumference, Cognitive Activities Scale, WHI Activities Scale; EPESE Activities. 3MS=Modified MMSE; CAM= Confusion Assessment Method; MDAS= Memorial Delirium Assessment Scale; DSI=delirium symptom interview; DRS= Dementia Rating Scale; DQ=Dementia Questionnaire; WTAR= Wechsler Test of Adult Reading; ADL = Activities of Daily Living; IADL= Instrumental Activities of Daily Living; Na=sodium; K=potassium; Glu=glucose; Hct=hematocrit; Alb=albumin; BUN/Cr= Blood urea nitrogen to creatinine ratio; APACHE=Acute Physiology, Age and Chronic Health Evaluation; HTN=hypertension; DM=diabetes mellitus; chol=hypercholesterolemia; VD=vascular disease; LOS=Length of hospital stay; GDS=Geriatric Depression Scale; INT= patient interview; MR= medical record abstraction; FAM=family/caregiver interview; LAB=blood testing; RN INT=nursing staff interview; NDI=National Death Index (including death certificate information).

A.9. Procedures for the Project 5. Feasibility Interview:

A.9.1.Subject selection: 100 currently enrolled SAGES participants will take part in the Project 5 Feasibility Interview. Participants will be called by a SAGES team member as part of a routine study call and asked if they would be willing to participant in the Project 5 Feasibility interview during a phone call. Participants who express interest in the survey will then be consented on the phone using verbal consent procedures and the feasibility interview will be administered.

A9.1.2 Instruments: Participants who consent to take part will be given a 20 minute phone survey using standardized questions with multiple-choice and short response questions.

A.10 Procedures for the Project 6—SAGES Harvard Initiative on Aging Pilot: Exploring Molecular Mechanisms of Frailty:

A.10.1 Subject Selection: The frail group will be selected as the most frail in the remaining SAGES I orthopedic surgery population (scores of 4-5), with gradually progressive trajectory over follow-up. The non-frail (robust) group will be selected as those without frailty indicators (scores of 0-1) with generally non-frail scores over all follow-up periods (scores of 0-2, and remaining at score=0 at final follow up). We will select participants to have mean age as close as possible between the frail and non-frail groups.

A10.2. Instruments, procedures and blood acquisition: We will utilize the frailty questions and assessments that are already in our assessment battery and described above, including weight & height, SF 12 questions, Minnesota leisure time, grip strength and timed walk.

We conduct an additional frailty assessment and will collect in total20ml blood from each participants. Blood samples will be collected into sterile vacuum tubes using either a vacutainer or butterfly system, at the preference of the phlebotomist. Blood will be drawn by a trained member of our research team.

12 ml of the blood will be delivered to the Harvard Stem Cell Institute (HSCI) iPS Core Facility is a service center located in Bauer Building, Room B01, 7 Divinity Avenue,
Cambridge, MA 02138 that we will contract with for the derivation of iPS cell lines from the donor samples.
8 mlof blood will be delivered to the CRC at BIDMC

All samples provided to the iPS Core or BIDMC for derivation will be coded. The iPS Core and study investigators will never receive any donor identifiable information. The iPS Core and BIDMC CRC will use their standard operating procedures and protocols for derivation and characterization services provided.

B. Statistical Considerations

B.1. Sample Size Justification:

Our sample size was chosen based on an iterative process involving determining the size of the target population eligible, feasibility constraints, and then verifying adequate power to test the hypotheses across all of our proposed studies, Projects 1-4. Through these detailed considerations, and input from our expert statisticians, we have been able to verify adequate power to address all of our study aims with the proposed sample sizes of 550 surgical patients and 120 non-surgical controls. We have presented power calculations for each of primary aims of the studies below. Power has similarly been verified for all aims of each project.

B.1.1. Sample Size for Project 1. For Project 1 (epidemiologic outcomes study), the power calculation for our primary outcome (cognitive decline by our summary cognitive measure) was examined as follows. Hypothesis 1 tests whether the degree of cognitive decline is higher in the delirium group, compared with the non-delirium group at 18 months. Estimates of effect sizes are drawn from Francis et al. (*Francis 1992*) who found that a sample of delirious patients declined over 2 years on MMSE performance from a baseline mean (SD) of 27 (3.3) to 23.7 (5.1), while a control sample declined from a baseline mean of 27 (2.4) to 26.4 (4.2). The net decline attributable to delirium is -2.7 MMSE points, or -0.82 standard deviation units. McCusker et al *(McCusker 2001)* report a similar magnitude of decline for delirious patients (-3.3 MMSE points). Extrapolating the more conservative Francis et al estimate to 18 months (the follow-up interval for the current study), leads to a net difference of -0.61 SD units for persons with delirium. For power calculations we use a worst case scenario using only those subjects with observations at all follow-up times. We expect that an initial cohort of 500 participants will be hospitalized and undergo surgery. Using attrition and refusal rates derived from our previous studies in similar study populations, we expect the number of subjects with complete observations at 18 months to be 400 [*Note*: we do not intend to use a list-wise complete analysis framework, but such a framework serves as a conservative lower bound for estimates of statistical power relative to more powerful and appropriate methods taking a principled approach to missing data]. Assuming (1) 25% of hospitalized elders in our cohort experience delirium during hospitalization and (2) Type-I error of 5%, we estimate that we will have 100% power to detect an effect as large as -0.61 SD units. We will have >80% power to detect effects as small as -0.33 SD units. The minimal detectable effect size lies between what are classified as small (ES = -0.20) and medium (ES = -0.50) effect sizes in Cohen's taxonomy *(Cohen 1988).* Medium and larger effect sizes are suggested as the lower bound of effects that are of clinical significance *(Cohen 1988, Norman 2003)*. Therefore, despite anticipated attrition, we will have excellent power to detect our hypothesized effect. While confounders may weaken the effect size, we still have >80% power to detect a reduction of effect size by as much as 46% (to -0.61 relative to -0.33).

For secondary analyses, we propose to examine the cognitive trajectory up to 36-month follow-up. Prorating the Francis estimate to 36 months, yields a net difference of -1.5 SD units for persons with delirium. A conservative estimate on statistical power can be based on the anticipated complete sample of 53 of the 500 surgical patients available at follow-up month 36 (213 are censored due to truncated follow-up; the rest due to death and other losses). Assuming a cumulative incidence of delirium of 25% and a Type-I error of 5%, we estimate that we will have 99% power to detect an effect as large as -1.5 SD units; we will have >80% power to detect effects of -0.91 SD units. Thus, despite attrition, we anticipate good power to test our secondary aims.

Sample Size for the Nonsurgical Comparison Group: The nonsurgical comparison group (N= 120) is utilized only by Projects 1 and 4. Its main purpose is to quantify normal age-related changes, and to quantify retest (learning) effects on cognitive testing over time. The sample size is justified in that with N=120, assuming a large correlation (r=.80) of baseline and repeat testing, and a moderate retest effect (standardized difference of 0.50 units), the probable (standard) error of the mean retest effect is about 10% of a standard deviation. This level of precision is sufficient to quantify the magnitude of retest effects, which are not a primary focus but important to define and statistically isolate from the other main effects (surgery, delirium and their interactions with longer-term decline).

Similar studies have also used samples of 120 as comparison groups

B.1.1.2 Sample Size for Project 1 Sub-study: Our goal is to enroll 240 patients with or without cognitive decline for this sub-study. For the clinical outcomes sub-study, over the next year, we anticipate a total of 256 patients will reach the 6-, 12-, or 18-month follow-up assessments. We estimate that 25-50 patients, or 10-20% of those achieving the 6-18 month follow up thresholds, will meet the above criteria and require clinical examinations over the supplement year. The 10-20% figure is considered to be a reliable estimate based on prior studies in the literature (Bickel 2008,, as well as our preliminary experience using our primary cognitive outcome, the general cognitive performance measure (GCP), where we find that of 45 study subjects who have completed 6 months of follow-up, 13% show a reliable decline in cognitive performance

B.1.1.3 Sample Size for Project 1 Validation study: Our goal is to enroll 50 patients over 2 years from the SAGES study cohort who are in the follow-up phase. Validation testing will occur once.

B.1.1.4 Sample Size for Project 1 Pain-Delirium sub-study: Our goal is to include all surgical patients from the SAGES study cohort. All patients provided written consent to review their medical charts.

B.1.2. Sample Size for Project 2. For Project 2 (biomarkers study), we will use principal component analysis to examine the relationship of biomarkers to delirium at each of the four time points in the biomarker discovery sample (N=100). Due to lack of information on the distribution of cytokine principal components, we computed power based on a fraction of the standard deviation. We used PROC POWER from SAS/STAT software. The power estimate is based on the 2-tailed 2-sample t-test for testing a difference between the absolute difference of the mean level of the biomarker principal component between those with and without delirium with Type-I error set at 0.05. The other factor that influences power is the degree of correlation of biomarker levels within matched pairs relative to the overall sample. This represents the ability of the matching procedure to remove “noise” with regard to confounders and focus the analysis on the key variable: the presence or absence of delirium. We performed the power analysis with a worst case scenario (no correlation), and best case scenario (moderate correlation, Pearson r=0.3). Our power calculations demonstrate that we can detect 0.57 S.D. unit differences (medium effect) under the worst case scenario and a 0.26 SD unit (small effect) differences under the best case scenario between delirium and non-delirium groups with 80% power. These are small to medium effect sizes and well below the differences in biomarkers seen in our pilot data. Therefore, we have good to excellent power for our biomarker discovery aims.

B.1.3. Sample Size for Project 3. For Project 3 (neuroimaging study), we proposed to examine a subgroup of the study cohort of 150 older surgical patients. We chose to only examine a subgroup due to expense and feasibility constraints. The justification for this sample size is as follows. Since the hypotheses for this aim concern the cumulative risk for developing delirium during hospitalization, the analysis can be approached with logistic regression, with the occurrence of delirium as the outcome and the measures of brain volume or blood flow as predictor variables. This analysis will make use of the entire cohort of 150 persons scanned, in which we anticipate a 40% or greater cumulative risk of delirium based on preliminary data [Note: while other projects assume a 25% cumulative risk of delirium, this project uses a selection algorithm to select a subset of subjects at higher risk of delirium for the neuroimaging study]. The expected effect size of an odds ratio of 2 that can be detected for the regression of a binary outcome (delirium) on a change of one standard deviation of the continuous predictor variable (CSF volume, or white matter hyperintensity, or global blood flow) with Type-I error level of 5% and power of 80% (a Type-II error level of 20%), was determined using the method proposed by Tosteson et al. (*Tosteson 2003*) For the effect size of an odds ratio of 2.0 that we assume is comparable to reported odds ratio estimates between 2.5 and 8.3 for clinical risk factors associated with delirium by Marcantonio et al. (*Marcantonio 1994 JAMA*), we would need a sample size of 81.

B.1.4. Sample Size for Project 4. Project 4 (cognitive reserve study) represents descriptive, exploratory work to develop a new measure of cognitive reserve for delirium; it is a secondary data analysis study. Models to define measurement properties of reserve indicators will

make use of all planned baseline assessments (n = 670, including 550 surgical patients and 120 non-surgical comparison group members). Although actual required sample sizes for stable parameter estimation vary according to aspects of individual studies (number and scale of variables, level of covariation, number of presumed latent variables), our sample size lies in the range of “very good” (n = 500) to “excellent” (n = 1000) minimal sample size requirements for factor analysis work.

B.1.5.Sample Size for Project 5. For the Feasibility Interview, the sample size of 100 was selected to enable robust estimates of the percent of SAGES participants willing to undergo these procedures.

B.1.6. Sample Size for Project 6. Due to budgetary constraints of generating the cell lines and running assays across 5 laboratories, we will include a convenience sample of only up to 30 orthopedic surgery participants (~15 frail and ~15 non-frail) for this pilot study.

B.2. Data Analysis.

The Data Management and Statistical Analysis (DMSA) Core (Core C) will provide data management services, statistical analyses and collaboration to the other Cores and Projects in the Program Project. The primary responsibilities of the DMSA Core will be to develop information systems and software for tracking participants, receiving, management and cleaning of data, generation of data sets, and performing statistical analyses tied to the specific aims of the projects. The specific aims for this Core are: 1. To generate information systems and software for tracking participants and flow of data; 2. To assemble and manage a database of longitudinal information collected from participants during screening, follow up and the conduct of individual projects; 3. To collaborate with the Epidemiology Core and Project Leaders in all phases of study design including determining the sampling scheme for the study, addressing non-response and providing real-time selection, enrollment, and matching as needed for substudies (Project 3); 4. To provide methodologic and analytic expertise to Project Investigators including study design and conduct, development and implementation of data analytical plans, interpretation of statistical results and manuscript preparation; 5. To lead analyses of variables collected by the Epidemiology Core and individual research projects; and 6. To develop composites for cognition and functional outcomes. Senior leadership for the Core will be provided by L. Adrienne Cupples, PhD, Professor and former Chair of the Department of Biostatistics at Boston University School of Public Health. Day-to-day and operational leadership will be provided by Richard N. Jones, ScD, located at the Institute for Aging Research (IFAR) of the Hebrew Rehabilitation Center (HRC). Dr. Long Ngo (BIDMC) will also serve as coinvestigator and member of this Core. Data will be stored and analyzed at the Hebrew Rehabilitation Center.

Table 3 provides a brief description of each Project's hypotheses and a general indication of the analytic approach. Projects 1-4 have hypotheses that involve change, including change in binary variables (occurrence of delirium, a non-absorbing state) or change in cognition. A general approach to the analysis of longitudinal data of this kind is the general linear mixed model (GLMM). Survival models (e.g., Cox proportional hazards, frailty, and discrete time survival models) could also be used for binary events if they are assumed to be absorbing (e.g., time to first delirium). Parameters for such models can be estimated with a variety of different software packages to yield varying classes of models used for change studies: individual growth curve models; random coefficient models; multilevel models; mixed models; or hierarchical linear models.

We will consider several approaches to account for missing data in our study, including maximum likelihood methods that model the missingness and imputation. One approach uses a random effects model for the outcome measurement, where the random effect represents the subject-specific effect. A second possible approach is the random-coefficient selection model that allows subject drop-out to depend on missing values of the outcome variable. Still another approach will be multiple imputation methods. Applying these multiple methods will allow us to assess the degree to which our inferences are robust to different methods for handling missing data. If findings are consistent across methods, we will be reassured about the robustness of our findings. If findings are not consistent, then these multiple methods allow us to further explore the inconsistency and to decide on the best approach.

Project 5 data will be analyzed using summery and descriptive statistics.

Project 6 data will be analyzed at the following 5 Harvard labs:
Neutrons: Yankner lab will differentiate the iPS cells into neurons and probe neurophysiologic differences. Muscle cells: The Wagers lab will differentiate the iPS cells into muscle cells and probe physiologic differences at the molecular level. Mitochondrial function: The Haigis lab will explore differences in mitochondrial functioning, applying metabolomic and other molecular approaches.

Nicotinamide adenine dinucleotide (NAD) function: The Sinclair lab will explore differences in oxidative functioning particularly in relationship to NAD function. The Libermann lab (BIDMC) will assess inflammatory markers.

Generation of IPSCs: The HSCI iPS Core Facility will derive and characterize iPSC lines on a fee-for-service basis. The iPS Core has extensive experience in iPSC derivation from human blood using all current methods of reprogramming. The Core offers both derivation and characterization services so that the appropriate quality control measures can be put in place to ensure quality iPSC lines. The Yankner and Eggan labs will maintain the primary IPSC lines. The intent will be to eventually deposit these iPSC lines in a biorepository that has experience with banking and distributing human pluripotent stem cells. These labs have considerable experience in the manipulation and analysis of IPSC lines. We anticipate that these IPSC lines will be a valuable resource not only for this study but for the aging research community at large.

Table 3. Overview of Project Hypotheses and Analytic Approaches.

Project	Aim or Hypothesis	Outcome(s)	Predictor(s)	Approach(es)	NSC	Effect of Interest
1	Aim 1-2	Cognitive decline	Delirium Delirium Severity	GLMM	*	Time by delirium interaction
	Aim 3	Functional decline and health care utilization	Delirium	GLMM	*	Time by delirium interaction
2	Aim 1	Delirium	Cytokine signature	PCA, CLR		Cytokine profile dif. by delirium
	Aim 2	Delirium	Protein signature	SVM, PCA, CLR		Protein profile dif. by delirium
	Aim 3	Cognitive, functional decline	Cytokine/Protein signature	GLMM	○	Reg. of change on predictor
3	H 1.1	Delirium incidence	Fractional CSF volume	GLM		Reg. of outcome on predictor
	H 1.2	Delirium incidence	WMH volume	GLM		Reg. of outcome on predictor
	H 1.3	Delirium incidence	Global blood flow	GLM		Reg. of outcome on predictor
	H 2.1-3	Change in neuroimaging marker‡	Delirium	GLMM		Reg. of outcome on predictor
	H 3.1-2	Neuroimaging marker‡	GCP Biomarker signature	GLM		Reg. of outcome on predictor
	H 3.3	Delirium incidence, Cognitive decline	Neuroimaging marker ×Cognitive Reserve†	GLMM	○	Effect modification of neuroimaging marker‡ x Cognitive reserve†
4	Aim 2, H 1	Delirium incidence	Reserve†	GLM, DTS		Reg. of outcome on predictor
	Aim 3, H 2-3	Cognitive, Functional decline	Reserve†	GLMM, LGC	*	Reg. of outcome on predictor

CLR = Conditional Logistic Regression; CSF = Cerebro-Spinal Fluid; DTS = Discrete Time Survival analysis, including cumulative risk models; GLM = Generalized Linear Model (including linear regression, ANOVA, logistic regression, longitudinal conditional logistic regression); GLMM = General Linear Mixed Model; GCP = General Cognitive Performance; LGC = Latent Growth Curve; NSC = Non-surgical comparison group; PCA = Principal Components Analysis; SVM = Support Vector Machines; Reg. = regression; WMH = White Matter Hyperintensity. † Project 3 H 3.3 is distinct from Project 4 H1, H2 by the exclusive focus on cognitive/behavioral aspects of reserve in the predictor. Project 4 includes brain imaging parameters in the general reserve concept. ‡ Neuroimaging markers are brain volume, white matter hyperintensities, and global blood flow (perfusion). * indicates analyses where simultaneous modeling of NSC and surgical patients will be used to statistically separate retest/learning, surgical, delirium and long-term cognitive decline. ○ indicates analyses of cognitive or functional change when repeatedly observed cognitive and functional performance will be residualized with respect to NSC (Non-surgical comparison group) change estimates (i.e., subtract mean NSC retest effects from observed performance).

C. Subject Selection

C.1. Inclusion Criteria: The surgical procedures selected are those which are associated with a high risk (>25%) of delirium, i.e., total hip or knee replacement, cervical laminectomy, lumbar laminectomy, lower extremity arterial bypass, thoracoabdominal aortic aneurysm repair**,** open abdominal aortic aneurysm repair, lower extremity amputation, or colectomy. The published literature indicates a high risk of delirium associated with vascular and orthopedic surgery and colectomy (*Balasundaram 2007, Benoit 2005, Bohner 2003, Galanakis 2001, Ganai 2007, Kudoh 2004, Mann 2000, Marcantonio/Goldman 1994, Olin 2005, Sampson 2007, Schneider 2002*). We have reduced the number of surgical types in order to reduce the heterogeneity of risks in our study population. In addition, some high-risk procedures from these categories were excluded. Coronary artery bypass surgery was excluded, since this surgery is associated with long-term cognitive decline due to microemboli and other phenomena associated with the cardiac bypass pump. Similarly, carotid endarterectomy was excluded due to associated microembolic phenomena. Hip fracture surgery was excluded due to its non-elective nature. For this study, potential subjects will be identified from the BIDMC and BWH operating room advanced booking schedules.

C.1.1. The specific eligibility criteria are as follows: (1) Age ≥ 70 years; (2) scheduled for an elective major vascular or orthopedic surgical procedure or colectomy (open, not minimally invasive); (3) planned to receive general anesthesia and to be admitted to the hospital for at least 2 days; (4) scheduled at least 7 days prior to surgery, to allow adequate time for the baseline assessment; (5) English-speaking.

C.1.2. Exclusionary criteria are: (1) Probable dementia, other than mild impairment (by 3MS): we will implement a two-stage process to exclude all patients with probable dementia, mild-moderate impairment or greater at baseline (see details below); (2) active delirium by medical record review or initial cognitive testing; (3) any hospitalization within 3 months prior to enrollment—to minimize the risk of delirium in previous 3 months; (4) terminal condition (i.e., life expectancy < 6 months), including terminal diagnoses such as metastatic cancer, pancreatic cancer, or receiving palliative care; (5) heavy alcohol history—due to the risk of delirium tremens including documented evidence of alcohol abuse or history of alcohol withdrawal within last 6 months, and greater than 5 drinks per day (for men) or greater than 4 drinks per day (for women); (6) legal blindness and total deafness due to inability to complete neuropsychological testing (lesser degrees of vision/hearing impairment will be included); (7) History of schizophrenia or psychosis; (8) Current chemotherapy;

In the first stage of our dementia screening process, we will exclude all patients with a history of dementia or use of dementia drugs by medical record review or physician report, or with a 3MS score of <69 or its education-adjusted equivalent (correlates with MMSE score ≤ 20) on the screening interview (*Tombaugh 1996).* The education-adjusted scores (*Khachaturian 2000*) are ≤60, ≤66, ≤69, ≤70, ≤72, ≤73 for persons with <8, 8-11, 12, 13-15, 16, 17+ years of education, respectively. For the second stage (baseline interview), patients scoring in the abnormal range on any 2 tests (> 1 SD below mean) in the neuropsychological battery will be adjudicated by an expert panel including 2 neurologists, 1 neuropsychologist, 1 geriatric psychiatrist and 2 geriatricians, with review of all study data including interviews, neuropsychological testing results, informant- rated Dementia Questionnaire (DQ, *Silverman 1987*) where available, and medical record data. The expert panel members will review cases quarterly. This 2-stage process should allow us to identify all patients with probable dementia.

See **Section A.5.1** for selection of MRI substudy patients. Additional exclusions for the MRI substudy are any contraindication to MRI which may include the following: 1. Pacemaker; 2. MRI incompatible metal implant; 3. Recently implanted vascular clip; 4. History of claustrophobia; 5. Metal fragment within the eye. Because of the age-range of our study population (age 70 and older), there will not be any pregnant women in our sample.

C.1.3. Non-surgical Comparison Group: Other than the requirement for surgery, the comparison group will meet the same inclusion and exclusion criteria listed above. The comparison group will also be matched to the surgical cohort using a computerized prospective frequency-matching algorithm for age, gender, education, baseline cognitive function, and comorbidities. Success of matching will be monitored regularly, and adjustments for imbalances will be made.

C.2. Inclusion of Women, Minorities, and Children: Gender and minority representation will be present in the study sample-projected enrollment figures are presented below. We will put into place steps to enhance minority recruitment and retention. In our previous work, the investigators have been able to recruit a study sample of similar racial/ethnic background to the overall eligible population. Children will not be included in the sample, since the study is designed to examine cognitive outcomes in older adults. In addition, because of our targeted elderly age group, no women of childbearing age will be included in the sample.

Project 6 inclusion: up to 30 orthopedic surgery participants from the SAGES study (15 frail and 15 non-frail) will be selected for this pilot study. Initial eligibility will be established by SAGES participants frailty status from previous frailly assessments. Then eligible participants who previously gave permission to be approach for other studies, who passed the SAGES capacity assessment and who provide written consent for this sub-study will be included and another frailty assessment will be performed. If the current frailty status is within the eligibility range described previously phlebotomy will be performed.

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	11	3	14
Not Hispanic or Latino	341	245	586
Ethnic Category: Total of All Subjects *	352	248	600
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	87	39	126
White	263	207	470
Racial Categories: Total of All Subjects *	352	248	600

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.” Estimates based on our Pilot Studies.

B4. POSSIBLE BENEFITS

B.4.1. **Potential Benefits**

This study is being performed to advance medical knowledge. Although participants in previous similar research studies performed by the study investigators have generally enjoyed their interactions with study personnel, we cannot guarantee any direct benefit will accrue to study participants. Given the burden of data collection required, we have made provision for modest subject incentives for participation in the study. These will be disbursed as follows: $40 for completion of the baseline assessment, $20 for each proxy interview, $40 for completion of all in-hospital assessments, $40 for completion of the one-month assessment (including phlebotomy), and $30 for completion of each face-to-face follow-up assessment (2, 6, 12, 18 months and every 6 months to 12 years). Given the larger time commitments, larger stipends of $100 per scan will be provided for the neuroimaging study (Project 3).

For Project 5, participation in the feasibility interview will be reimbursed with $20.

For Project 6, participation will be reimbursed with $30 for the functional status assessment, and $75 for the blood draw.

B.4.2. **Importance of the Knowledge to be Gained**

Given the common, serious, and potentially preventable nature of delirium, establishing its long-term outcomes is key to moving the field ahead. If delirium does contribute independently to adverse effects on long-term cognitive and functional outcomes, the results of the proposed work will motivate future intervention studies to address this important area. This study will provide substantial advances over previous work, including the state-of-the-measurement of delirium and cognitive decline, large sample size, baseline assessment pre-delirium, frequent follow-up assessments, and control for competing causes. This study provides an innovative conceptualization of delirium as a potential reversible cause of cognitive and functional decline, and represents an initial step in generating novel strategies to forestall such decline in late life.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

B.5.1. Possible Risks of the Study

Overall, this study is a minimal risk study by NIH criteria. The sources of risk are of 4 types in this study: participation in the interviews, risk of breach of confidential information, risk of phlebotomy (Project 2), and risk of MRI (Project 3). The first "risk" of the study is the time necessary to participate in the study interviews and assessments. In our prior experience, patients view interactions with the research staff as very positive and enjoyable, however, some of the interviews may pose the risk of fatigue or emotional distress, particularly while the patients are hospitalized. Should a subject become tired or distraught, the interview will be halted.

A related "risk" of participation is the potential for breach of confidentiality and privacy of Protected Health Information. Methods to reduce or eliminate this risk are described below. In addition, knowledge of a patient's genetic status with regard to the ApoE-ε4 allele (Project 2) may be a source of emotional stress to the patient or their family. Therefore, the informed consent will state that ApoE genotyping results and the results of any additional genetic testing performed on the bio-repository will not be shared with the patients and/or his/her family, and will not become part of the medical record. All interviewers will undergo extensive training in general principles of informed consent, confidentiality, and administering research instruments in a humane, reliable, and valid manner.

A third "risk" of participation is the risk of phlebotomy to obtain serum for the serum biomarker assays at 4 time points during the study. Wherever possible (and this will be for the majority of cases), the serum collection will be obtained at the same time as phlebotomy for routine clinical laboratory work, thereby, eliminating an additional risk imposed by a separate phlebotomy for study purposes. When this is not possible, then the phlebotomy will be performed by a trained member of the study team. The risks of the phlebotomy procedure itself are minimal, and are primarily related to pain or bruising at the needle puncture site. Since the amount of blood required at each time point is small the risks from anemia or blood loss are negligible. The blood draws will total only 90 ml over a minimum of 6 weeks, which is considered minimal risk. As an added safeguard, participants with a baseline hematocrit of under 30% but above 24% will have one less tube of blood collected at each time point, resulting in a total of 50 cc of blood across the 4 time points. Patients with a baseline hematocrit of less than 24% will be excluded from the study.

The fourth "risk" of participation pertains to participation in the MRI (n=150) and the Project 1 sub-study study (n=240). The risks of MRI scanning are minimal. Prior to entering the MRI scanner, subjects will complete a standard pre-MRI checklist to screen for the presence of implanted metals or other conditions that would preclude them from safely entering the high-field magnetic environment. The most common discomforts associated with MRI are due to either symptoms of claustrophobia or the loud sounds generated in the MRI environment. No radiation or contrast (i.e., no gadolinium) will be used for these scans. All imaging sequences will be within the FDA guidelines for radiofrequency (RF) power deposition and magnetic field switching. For patients of the Project 1 sub-study who are not eligible for the MRI, a computed tomography (CT) will be offered which may involve exposure to radiation from one low-dose CT scan (1.3 mSv). This dose is minimal and equivalent to five months radiation exposure from natural sources. One possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The increase in the chance of getting a fatal cancer, as a result of the radiation may be estimated to increase from 25 percent to 25.01%. This change in risk is small and cannot be measured directly.

The fifth "risk" of participation includes potential pain related to the grip strength test and falls related to the timed walk. To avoid these risks participants will be excluded from the grip strength test if they report pain, arthritis, or tendonitis. Prior to the timed walk participants will be asked if they feel comfortable performing this test. If either the participant or the interviewer feels that a timed walk would not be safe, the test will not be performed.

Due to the study selection criteria (eliminating all persons with dementia), we anticipate that most patients will be able to provide informed consent. However, at baseline all patients will be assessed with a capacity form for their understanding of the study, the risks and benefits associated with the study, the voluntary nature of participation, and the confidential nature of all study data. If, at baseline, the research staff assess that the patient is not able to give informed consent, the patient will not be eligible for study participation. At each follow-up visit, capacity to give consent will be assessed again and if the patient is not able to give consent then consent from a legally authorized representative (spouse, adult child, parent, sibling, other relative or close friend) or a legal guardian. For the Project 1 sub-study, written informed consent will be received from both the patient and his/her legally authorized representative. Safeguards will be put into place to protect the rights of cognitively impaired participants.

Project 5 will not add any additional risk to this low risk study and will not change the risk benefit ratio.

Project 6 risks: The main risks are related to a potential for breach of confidentiality and privacy of Protected Health Information, the risks related to phlebotomy and risks related to the functional status

assessment (grip strength test and falls related to the timed walk), are described above. Additional risks related to the genetic research include the possibility that someone in the future could link donors' genetic or medical information back to the donor and if that information suggested something serious about a donor's health could be misused. Due to our de-identification procedures and strict data protection procedures, the risk of such a breach is negligible; the data will not be able to be traced back to the patient/donor.

If a subject wishes to withdraw from the study and the data that has already been collected/used, they will remain part of the study database and will not be removed in order to maintain the integrity of the research. At any time, a donor may ask to have their sample destroyed. We would then destroy any remaining portion of the samples directly donated by the donor, and destroy the link between the donor's identifying information and their samples. However, we will not destroy research data that has already been gathered using the samples, nor any stem cell lines already derived from the samples

Remaining blood samples would be discarded. After data has been generated, transferred to a repository or to another researcher, that data will remain intact. However, since the data is deidentified, it cannot be traced back to the patient.

B.5.2. Protection against Risks:

All study procedures will be conducted by trained clinical personnel, who will halt all interviews or procedures at the earliest sign of patient fatigue or distress, or at direct patient request. All interviews and procedures will be streamlined to minimize fatigue and inconvenience, and will be carefully timed to minimize interference with other activities, such as clinic appointments or hospital activities. In addition, ongoing training will be provided to the research staff throughout the study time course to minimize adverse events and risks. The participants will be provided with the contact information for the principal investigator and project director who will be available (or have coverage arranged) in case of unanticipated problems or psychological distress.

To safeguard confidentiality and privacy of protected health information, each study subject will be assigned a unique code number for the study, and the subject's name or identifiers will never be attached to any form, plasma sample, or genetic material. A separate file linking the patient's name with study number and identifiers will be kept in a password-protected data file, accessible only by trained, HIPAA-certified research staff. The data file will be stored on a password-protected server, and will not be stored on any portable media. All study forms will be deidentified kept in secure, locked file cabinets. The study investigators will assume full responsibility to maintain the confidentiality of all data. All study results will be presented only as statistical aggregates that will neither identify nor permit identification of individual subjects. We will follow Medicare/CMS approved data management procedures for storage, access, management, and analysis of the Medicare data. **https://www.instituteforagingresearch.org/resources/research-administration/ifar-research-compliance/data-protection**

If a study interviewer identifies delirium in the course of daily postoperative assessments, we will notify the primary care team by placing a 'flag' on or near the cover of the medical record. The flag will be a bright piece of paper designed and positioned in conjunction with our participating surgeons. It will state that, based on our research assessment, the patient meets Confusion Assessment Method (CAM) criteria for delirium on that day. We will update the flag on a daily basis, and remove it when the patient no longer meets CAM criteria. Since ours is a research-based assessment that will not be performed by a clinician, the flag will not be incorporated into the permanent medical record. Furthermore, our study team will not dictate further evaluation or treatment, which will be conducted at the discretion of the primary care team.

To protect against the risks of phlebotomy, all eligible research staff will be carefully trained in all procedures. Pressure will be held over the puncture site for an adequate time period to minimize bleeding. In addition, wherever possible, the bloods will be obtained along with other laboratories ordered for clinical care to minimize any extra phlebotomies. Because of the timing of the specimens, at baseline (clinic visit), hospital admission, day 2 during hospitalization, and one-month follow-up, the vast majority of blood work for the study will not require an extra phlebotomy. We will also put in precautions to protect patients with anemia. For patients with a hematocrit of <30%, we will reduce the amount of blood drawn to 50 ml. Patients with a hematocrit of <24% will be excluded.

All MRI scanners are operated within a controlled areas requiring key card access. Access is restricted to MR knowledgeable personnel with MRI safety training. All subjects must complete an extensive MRI screening questionnaire and technologists have been trained in contraindications to MRI and other MRI safety issues. To minimize risks from the MRI procedures, subjects will have voice contact with the technologist performing the study at all times, and the study can be terminated immediately as necessary. Subjects will be provided with earplugs to minimize any discomfort associated with noise in the MRI, and they will be informed that they can request the MRI scan to be terminated at any point due to discomfort or claustrophobia.

A MRI Safety Protocol will be followed to ensure standardized handling of incidental findings. This MRI Safety protocol has the purpose of providing clinical backup to MRI research staff for any unexpected medical issues that arise in the course of participants undergoing MRI scans and to manage incidental findings on MRI, including maintenance of a database of such findings. Our Safety Officer, Dr. Jeffrey Silverstein, will be informed about all incidental findings.

The grip strength will not be conducted with participants who report any pain or discomfort in their hand. The timed walk will not be conducted if participants are dizzy, unsteady or if the interviewer or participant feels unsafe. To protect against the risk of falling, trained interviewers will walk just behind the participant to guard against falling. If a person reports any pain the test will be stopped immediately.

We will implement safety monitoring procedures, including weekly meetings with the operations team, monthly meetings with the project working group, and semiannual meetings with our Safety Officer, to monitor and enhance the safety of all subjects in this study. All reports of adverse events will be directed immediately to the Principal Investigator (Dr. Inouye) and Core B Leader (Dr. Marcantonio), and will be attended to within 24 hours. Dr. Marcantonio will work closely to coordinate activities at the Brigham and Women's Hospital, and will oversee safety issues there. Serious adverse events will be reported to the Safety Officer and the NIH immediately. Although our study is not an interventional trial, it does involve substantial data collection burden, including phlebotomy and neuroimaging (for some patients). Therefore, an independent Safety Officer will be appointed for the duration of the study (See Part P for further details). He will review any adverse events related to subject participation, and make suggestions for corrective action, if necessary.

For project 6, data will use additional safeguard for the protection of subject's privacy. Each subject will be assigned a unique code that will be distinct from the codes used for the SAGES study. This Project 6 code will only be linked to the SAGES study code. The key linking the Project 6 code to the SAGES study code will be kept separate from other links on a firewall protected server at HSL. Only a selected, trained analyst will have access to the code. The subject's name or identifiers will never be attached to any form, data, plasma sample, or genetic material. None of the labs working with the biospecimens or research data will have access to the keys linking the specimens or data back to identifiable information. The link between identifiable donor information and the biospecimens and data will be destroyed after completion of the study.

B.5.3. Analysis of Risk/Benefit Ratio

Delirium remains a common, morbid, and costly problem among hospitalized elders. Yet, our understanding of its epidemiology and long-term outcomes remains limited, and there are no targeted treatments other than good general medical care. The proposed research will help to elucidate the long-term cognitive and functional outcomes independently associated with delirium, the role of biomarkers and neuroimaging in delirium, and the importance of cognitive reserve in delirium. On balance, the anticipated benefits to society from the knowledge to be gained far outweigh the minimal risks presented to the study subjects. Thus, the risks to subjects are reasonable in relationship to the anticipated benefits to future patients and to society; the risk-benefit ratio appears to be quite favorable for proceeding with the proposed Program Project.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

We have already obtained the support of the Chiefs of all Services from which eligible patients will be screened and enrolled. Prior to study initiation, we will send a letter to all attending physicians who admit patients to these services requesting permission to enroll their patients in this study. In our prior studies, between 98-100% of physicians have given their permission to enroll their patients. Since we have already obtained support of key leaders of each service, we anticipate similar high participation rate in the current study. If a particular physician refuses participation, his or her patients will be excluded from enrollment into the study.

Subjects will be identified by daily review of the operating room advanced booking schedules at both the BIDMC and BWH. The schedules include the patient's names and scheduled procedures. Patients meeting our criteria of age 70 and older and undergoing one of the eligible major surgical procedures will undergo further screening. Initial screening will be conducted using data from the electronic medical record. Patients who meet initial criteria will be asked for verbal consent to undergo a brief (5 minute) face-to-face screening assessment in the primary care clinics and preoperative surgical clinics and physician's offices related to the BIDMC and BWH by our trained research staff.

Consent

Those who meet full eligibility criteria after this assessment will be asked to provide informed consent for participation in the study using a written form approved by the Institutional Review Boards of BIDMC and BWH. Informed consent will be obtained by trained study personnel in person (either in the patient's choice of their homes or at a clinic visit) following standard protocols. These procedures have already been successfully applied in our pilot studies. The consent will include permission to obtain medical records from outside hospitals. This request for outside medical records is a procedure that has been approved previously by our IRBs and has been applied in previous studies. Participants are re-consented at each visits (including capacity assessment) and asked if they want to continue participation The study investigators and project coordinators will be available to the participants to answer any questions. A single consent form will be used for this study; the exception is Project 3, the neuroimaging study, which will have its own (expanded) consent form due to the MRI, and for Project 1 Sub-study, clinical outcomes of delirium, which will have its own consent form due to the clinical examination. Project 1 Validation study will use verbal consent during a phone call. The activities of the Pain-Delirium study are covered with the main-study consent form. For Project 5 we will use verbal consent. Patients will be able to opt out or stop the interview any time. We included opt-in or opt-out questions for participant to indicate if they agree to allow health, blood, and MRI scan information to be stored for future studies. We re-consented all participants who are still active in the study for the main study and the MRI sub-sample.

Project 6 will use a separate consent form and only participants will be approached who previously indicated their willingness to participate in other research projects. Only participants who have capacity to consent and who provide written consent will be enrolled.

Subject Protection

Our study may involve the vulnerable population of cognitive impaired older persons. At baseline, due to our strict eligibility criteria excluding dementia patients, we anticipate that all of our study patients will be cognitively intact and able to give informed consent. At the time of each subsequent study assessment, we will seek assent from each patient for continued participation in the study. The patient may refuse continued participation at any time. If significant cognitive impairment develops during the course of this study, then assent for continued participation will also be sought from a family member or legal guardian. This dual procedure has been previously approved and successfully applied in our previous studies involving similar study populations.

B7. STUDY LOCATION

Privacy

The comfort and privacy of patients will be protected during every phase of the study by carefully trained research staff.

For the MRI Study (Project 3), All subjects being consented for the MRI exam will be met with in a private prep room in the Ansin 3rd Floor MRI Research area. All subjects will have the chance to have their questions answered by one of the study's investigators during this visit. The subject will then undergo MRI scan in the same research area.

Study Locations

Baseline and follow-up assessments will occur in the patient's choice of their homes or at a clinic visit. Space will be provided for interviewing in the BIDMC CRC if needed.

The in-hospital assessments will occur on the surgical units of BIDMC and BWH. The MRI scans will occur at BIDMC MRI Center.

The informed consent procedure and clinical examination for the Project 1 Sub-study will occur in the BIDMC Clinical Research Center. MRI or CT scans will be obtained in the BIDMC Outpatient Radiology Department, Shapiro 4th floor.

Project 5 will be administered over the phone.

The data analysis will occur at the Hebrew Rehabilitation Center (HRC).

Project 6 will be administered in participants' homes. Data analysis will occur at the following Harvard Labs: Yankner lab, Wagers lab, Haigis lab, Sinclair lab and Libermann lab (BIDMC). All labs will cede review to the BIDMC IRB via SMART IRB.

B8. DATA SECURITY

To safeguard confidentiality and privacy of protected health information (PHI), each study subject will be assigned a unique code number for the study, and the subject's name or identifiers will never be attached to any form, plasma sample, or genetic material. A separate file linking the patient's name with study number and identifiers will be kept in a password-protected data file, accessible only by study investigators. PHI will only be accessed at BIDMC or through remote access to the BIDMC system, protected by firewall. PHI will only be accessed by BIDMC faculty or staff and all staff have been trained as to HIPAA guidelines and requirements. The data file will be stored on a password-protected server, and will not be stored on any portable media. All study forms will be deidentified kept in secure, locked file cabinets, and will be shredded upon completion of the study analyses. The study investigators will assume full responsibility to maintain the confidentiality of all data. All study results will be presented only as statistical aggregates that will neither identify nor permit identification of individual subjects.

MRI/CT data: All hard copies of data acquired from the MRI will be kept in a locked cabinets to which only Dr. Alsop (Project Leader) or Dr. Fong (sub-study leader) and the research team will have access. All electronic records of the MRI will be stored on a secure server behind the BIDMC firewall. A copy of the electronic records will also be provided to co-investigators in charge of data analysis at the Hebrew Rehabilitation Center. Access to the database will require a login name and password. Patient identifiers will be kept separately and will be linked to the study data by a unique study ID. All patient identifiers will

be maintained for the duration of the study. After the required time period following the completion of the study, all paper-based documents will be destroyed using a shredder. All electronic documents bearing patient identifiers will be deleted.

All interview and medical record data will be stored and analyzed at the Hebrew Rehabilitation Center (HRC), under the leadership of Core C, our Data Management and Statistical Analysis Core. A secure server protected by multiple firewalls and passwords will be utilized to store the data according to HIPAA compliant guidelines.

B9 Multi-Site Studies

Is the BIDMC the coordinating site or is the BIDMC PI the lead investigator of the multi-site study?
☒ Yes ☐ No

THE BIDMC is the coordinating site, and Core B (Epidemiology Core), Project 2 (Biomarkers), Project 3 (Neuroimaging) are based at the BIDMC. The work of the 4 projects and 3 supporting cores, across 3 study sites, will be interconnected and synergistic, and will be coordinated through the Administrative Core (Core A). Under the leadership of Dr. Sharon Inouye (BIDMC investigator), this Core will provide the leadership and organization that will ensure integration, efficiency, and productivity; provide fiscal and budgetary management; verify scientific progress and adherence to timelines; provide safety monitoring; and coordinate all relevant meetings and reporting activities. The administrative components to achieve these goals will include the Steering Committee, meeting monthly to oversee the entire project; Operations Committee, meeting weekly to handle day-to-day progress of the cohort assembly and data collection; Fiscal Management Committee, meeting quarterly to oversee all budgets/subcontracts; Scientific Advisory Board, meeting yearly to evaluate progress; and a Safety Officer, meeting semiannually to oversee the safety monitoring plan.

B10 Dissemination of Research Results

We are sending out newsletters 1-2 times a year thanking participants for their participation. Whenever possible we will include progress and results of the study.

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