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Authors' contributions SKI conceptualized the original program project and cohort study. EMS, ERM, DCA, RNJ, and SKI made substantial contributions to the conception and design of the study, and were involved in drafting and revising the manuscript critically for important intellectual content. TGF, EM, SOR reviewed the manuscript critically for important intellectual content. All authors have given final approval of this manuscript to be published.

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Novel risk markers and long-term outcomes of delirium: The Successful Aging after Elective Surgery (SAGES) Study Design and Methods

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Abstract

Objectives—Delirium--a costly, life-threatening, and potentially preventable condition--is a common complication for older adults following major surgery. While the basic epidemiology of delirium after surgery has been defined, the contribution of delirium to long-term outcomes remains uncertain, and novel biomarkers from plasma and neuroimaging have yet to be examined. This program project was designed to contribute to our understanding of the complex multifactorial syndrome of delirium.

Design—Long-term prospective cohort study.

Setting—3 academic medical centers (2 hospitals and 1 coordinating center).

Participants—Patients without recognized dementia (targeted cohort = 550 patients) age 70 and older scheduled to undergo elective major surgery are assessed at baseline prior to surgery, daily during their hospital stay, and for 18-36 months after discharge.

Measurements—The Successful Aging after Elective Surgery (SAGES) study is an innovative, interdisciplinary study that includes biomarkers, neuroimaging, cognitive reserve markers, and serial neuropsychological testing to examine the contribution of delirium to long-term cognitive and functional decline. The primary goal is to examine the contribution of delirium to long-term cognitive and functional decline. In addition, novel risk markers, for delirium are being examined, including plasma biomarkers (e.g., cytokines, proteomics), advanced neuroimaging markers (e.g., volumetric, white matter hyperintensity, noncontrast blood flow, and diffusion tensor measures) and cognitive reserve markers (e.g., education, occupation, lifetime activities).

Conclusion—Results from this study will contribute to a fuller understanding of the etiology and prognosis of delirium. Ultimately, we hope this project will provide the groundwork for future

development of prevention and treatment strategies for delirium, designed to minimize the long-term negative impact of delirium in older adults.

Keywords

Delirium; Dementia; Surgery; Elderly; Long Term Outcomes; Risk Factors

INTRODUCTION

Delirium, an acute decline of cognition and attention, is a common, costly, life-threatening, and potentially preventable problem for older persons.^{1,2} As the most common complication of hospitalization and surgery, 15-53% of surgical patients develop delirium^{1,3} which in turn increases the risk of morbidity, functional decline, nursing home admission, prolonged length of hospital stay, and mortality.^{1,4,5} Hospital mortality rates following delirium range from 25-33%.^{5,6} Delirium accounts for over \$7 billion (2004 US dollars) of Medicare hospital expenditures¹ and additional costs of over \$118 billion per year (2011 dollars) for post-hospital medical costs, including post-acute care and rehabilitation services.⁷ Importantly, several previous studies have documented that at least 30-40% of delirium cases may be preventable through multicomponent intervention strategies.⁸⁻¹⁰

Despite its obvious clinical and health policy relevance, the etiology and long-term outcomes of delirium remain poorly understood. Delirium has been independently associated with long-term functional decline in a number of studies with follow-up periods ranging from 1 to 12 months in hip fracture¹¹⁻¹⁴, medical¹⁵⁻¹⁷, and long-term care¹⁸ patients. In another 4 studies, delirium did not demonstrate a significant impact on long-term functional outcomes at 3 months to 2 years follow-up.¹⁹⁻²² However, these studies have inconsistent results and many are limited by high attrition rates, infrequent follow-up, inclusion of moderate to severe dementia patients, lack of baseline pre-delirium assessment, lack of standardized follow-up testing, and inadequate control for competing causes of functional decline.

Whether delirium contributes *independently* to long-term or permanent cognitive impairment remains unclear, although the accumulating evidence is suggestive.^{1,4,5} Delirium symptoms can persist for months to years.^{3,23-26} Some causes of delirium, such as prolonged hypoxia or hypoglycemia, may lead to irreversible cognitive impairment.²⁷ Neuroimaging studies²⁸⁻³⁰ suggest that delirium may incite a derangement in brain vascular function that could lead to dementia in some cases. The entities of persistent delirium^{1,13,24} and reversible dementia³¹ blur the boundaries between these conditions. Moreover, delirium may herald the onset of dementia in some cases, as recognized frequently by clinicians and family members who point to examples where the delirium was “the beginning of the end”.

To address these gaps in knowledge, a group of interdisciplinary investigators launched a program project—Successful Aging after Elective Surgery (SAGES)—funded by the National Institute on Aging that aims to elucidate novel risk markers (including biomarkers, neuroimaging, and reserve markers) and to examine the contribution of delirium to long-term cognitive and functional decline. The program project grant (P01) mechanism is complex in scope and is intended to fund synergistic research designed to achieve results not attainable by investigators working independently <<http://grants1.nih.gov/grants/guide/pa-files/PAR-11-066.html>>. This mechanism is particularly suited for interdisciplinary investigators who wish to collaborate around a set of closely related projects addressing a distinct scientific problem. The present study is well-suited for this mechanism and provides substantial advances over previous work, including state-of-the-art measurement of delirium and cognitive decline, large sample size, baseline pre-delirium assessment, frequent follow-

up to 36 months, and careful examination of competing causes of long-term cognitive and functional decline. This program project provides an unprecedented opportunity to examine the etiology of this complex multifactorial geriatric syndrome. Upon completion, it will provide unique resources including a clinically rich database on a well-characterized cohort of 550 older persons prior to hospitalization or surgery with long-term follow-up (18-36 months), a library of advanced neuroimaging scans, and a biorepository of plasma and genetic material. Ultimately, we anticipate that this study will lay the groundwork to develop more effective prognostic, preventive, and treatment approaches for delirium following major surgery.

Conceptual Framework

A unifying conceptual framework for the study appears in Figure 1. Given the multifactorial nature of delirium, the investigation involves interdisciplinary approaches to clarify its epidemiology, risk markers, and prognosis. This study includes 4 projects which utilize the SAGES cohort and address inter-linked aims. Project 1 utilizes epidemiologic approaches to elucidate the long-term prognosis of delirium, specifically, its contributions to cognitive and functional decline. Project 2 uses laboratory approaches including multiplex analysis of cytokines and quantitative proteomics for discovery of biomarkers related to delirium. Project 3 employs advanced neuroimaging methods to identify imaging markers for delirium and to evaluate whether long-term neuroimaging changes (such as atrophy) are associated with delirium. Project 4 examines the role of cognitive and brain reserve in development and long-term outcomes of delirium.

METHODS

Overview

This 5-year prospective observational study examines 550 older patients prior to scheduled elective surgery, and thus, prior to the potential development of delirium. Patients are enrolled in the community, interviewed daily during the initial hospitalization for their surgery, and followed prospectively for a minimum of 18 months and up to 36 months after their initial hospitalization with a standardized battery of assessments including serial neuropsychological testing and physical functioning measures. Phlebotomy is performed at baseline, in the hospital (immediate post-operative and hospital day two), and at one-month after discharge. Approximately one-third of the sample receives MRI brain scans at baseline and one year later.

Eligibility

Study inclusion and exclusion criteria appear in Table 1. Older patients scheduled for elective major non-cardiac surgery are recruited from two Harvard-affiliated acute care teaching hospitals, Beth Israel Deaconess Medical Center (BIDMC) and Brigham and Women's Hospital (BWH), both in Boston, Massachusetts. The BIDMC has 601 beds with over 40,000 admissions, 750,000 outpatient visits, and 10,000 operations per year. The BWH has 747 beds with over 45,000 admissions, 754,000 outpatient visits, and 30,000 operations per year. The study originates from the Institute for Aging Research - Hebrew SeniorLife (HSL), a Harvard affiliate, which also serves as the field and data coordinating center.

Patients aged 70 or older who are scheduled for major elective orthopedic, vascular, or general surgical procedures with a moderate-to-high risk (>25%) of developing delirium (Table 1) are considered eligible³². Patients with active delirium or clinically recognized dementia are excluded. Dementia screening occurs at three levels: during initial medical record screening, telephone recruitment, and baseline enrollment interview. Patients who

have a diagnosis of dementia or who have documented dementia in the medical record are excluded. During telephone recruitment, patients are asked if they have ever received a diagnosis of dementia or Alzheimer's disease from a physician and are excluded if they answer affirmatively. At baseline interview, patients who fail a capacity assessment of their understanding of the informed consent are excluded. In addition, patients with a score of <69 or its education-adjusted equivalent on the Modified Mini-Mental (3MS) test during the baseline interview are excluded.³³ Finally, patients are assessed with the Confusion Assessment Method (CAM) for evidence of delirium and are excluded if delirium is present at baseline.³⁴ Detailed eligibility and exclusion criteria along with the associated procedures are indicated in Table 1. All study procedures are approved by the Institutional Review Boards (IRB) at the two clinical sites (BIDMC, BWH) and the coordinating center (HSL). Written informed consent was obtained from all participants.

To ensure high quality of all eligibility screening procedures, the medical records of all patients who are found to be study eligible are rescreened by a second staff member before patients are invited to participate in the study. In addition, random re-checks of the medical record screening are conducted on a monthly basis.

Recruitment

Informed by a feasibility study with high risk older adults that identified barriers to participation in long-term clinical research³⁵, recruitment and data collection procedures for SAGES include home-based assessments of less than 75 minutes in duration and free parking for all hospital-based activities. Only patients whose surgeons provided written approval to contact their patients are approached (86% of all eligible surgeons). The study staff reviews the BIDMC and BWH operating room advanced booking schedules twice weekly to identify eligible patients (Table 1). Patients who meet eligibility criteria receive a letter co-signed by their surgeon and the study investigators inviting them to participate in the study. Eligible patients are contacted by telephone to explain the study and confirm eligibility. Subsequently, patients are scheduled for a face-to-face baseline screening and assessment in their home, the hospital, or other location of their choice. During the baseline interview, eligible patients are offered participation in the MRI sub-study with a separate screening and consent procedure. Study enrollment is confirmed once an eligible surgery has been completed, and the operative date represents the zero-time for this prospective cohort study.

Study Assessments and Schedule

Interviews—Study participants undergo a baseline assessment prior to the index hospitalization, including neuropsychological testing and functional assessment. During the index hospitalization, patients are assessed daily for the development of delirium from the day after surgery until the day of discharge. After discharge, patients are followed with home-based interviews at 1 month, 2 months, and every 6 months up to 36 months to evaluate for all primary and secondary outcomes (described below). Brief telephone interviews are conducted in between face-to-face interviews at 4, 9, 15, 21, and 27 months to assess for delirium, functional status, hospitalization, or institutionalization. At baseline and every six months after the index hospitalization, proxies are interviewed by telephone for proxy ratings of cognitive and functional status and to report on hospitalization or institutionalization. Medical records are reviewed at the end of the index hospitalization and for all hospitalizations up to 18-36 months to identify recurrent delirium and new illnesses. Table 2 lists all outcomes variables and the study assessment schedule.

All study interviews are conducted by experienced interviewers, who undergo 2-4 weeks of intensive training and standardization. Each trainee is instructed by an expert interviewer on

how to administer questionnaires, then the trainee practices with peers and older adult volunteers. Once comfortable, trainees shadow an expert during 4-5 interviews with patients, and then trainees perform 4-5 interviews under observation by the expert interviewer. Both the trainee and expert score the interview, and after each shadowing session the trainee and expert discuss and resolve discrepancies. The training continues until a trainee has conducted two consecutive interviews without errors. Inter-rater reliability assessment and standardization on all key study variables is conducted every 6 months continually throughout the study. In addition, coding questions are addressed in weekly meetings of all study staff.

Medical Record Review—As an initial step, medical records are reviewed for eligibility screening (Table 1). After discharge from the index hospitalization, a comprehensive medical record abstraction is then conducted to provide information on the surgical procedure, anesthesia type and duration, baseline diagnoses and comorbidity, abnormal laboratory results, development of delirium, precipitating factors for delirium (e.g., medications, iatrogenic events, catheters or physical restraints), postoperative complications, intercurrent illnesses, and death. Subsequently, information on rehospitalization is obtained at any follow-up interview (patient or proxy). Additional chart reviews are planned of all hospitalizations to assess for recurrent delirium and inter-current illnesses. Inter-reliability assessment on chart review is planned for 10% of the sample.

Delirium Assessment

All 4 component projects of the program project use delirium as a major predictor, key outcome, or control variable. Delirium is assessed prospectively at baseline, daily during the index hospitalization, and at each follow-up interview based on information from the patient interviews including a brief cognitive screen (orientation, short-term recall, verbal fluency), digit span testing, Confusion Assessment Method (CAM), and Delirium Symptom Interview (DSI) and information on any acute changes noted from the nurse or family. The Delirium Symptom Interview (DSI)³⁶ is a brief instrument that is used specifically to determine the presence or absence of 8 key features of delirium and to inform the CAM rating. The presence of delirium is determined by fulfillment of the validated Confusion Assessment Method (CAM) diagnostic algorithm.³⁴ The CAM provides a widely used standardized method for identification of delirium, which has been demonstrated to have a sensitivity of 94% (95% confidence interval [CI] 91-97%), specificity of 89% (95% CI 85-94%), and inter-rater reliability of 0.70 to 1.00 in studies involving over 1,070 patients.³⁷ The methods for delirium identification used in this study have been widely applied and demonstrated to have high reliability in previous studies.^{6,38} Delirium by interviewer rating (CAM criteria) is further augmented with a validated delirium assessment from medical record review during the index hospitalization,³⁹ since delirium fluctuates and may occur between interviews. Delirium severity is rated with the widely-used Memorial Delirium Assessment Scale (MDAS),⁴⁰ a 10-item scale that uses information from cognitive testing and structured observations to rate delirium severity. Each item is rated as 0-3, to generate a 0-30 scale (30=most severe).

Delirium duration is defined as the total number of delirium-days with positive CAM rating during the index hospitalization. Delirium recurrence is defined as the total number of delirium episodes, which must be separated in time by at least 48 hours. Persistent delirium is assessed with a face-to-face or telephone interview 2 weeks after hospital admission in patients who had delirium during index hospitalization. Recurrent and persistent delirium will be handled as time-varying covariates in secondary analyses.

Primary Outcomes

The primary long-term outcomes for the program project include cognitive performance and physical functioning variables. These outcomes are assessed by a separate follow-up team which is blinded to the patient's delirium status during hospitalization.

General Cognitive Performance (GCP) Composite—A General Cognitive Performance (GCP) composite was created for this study. It represents a combination of neuropsychological measures and will be applied in our analyses as a continuous outcome measure.⁴¹ The complete neuropsychological test battery is described in Table 3 and includes the Hopkins Verbal Learning Test (HVLT), Digit Span Forwards and Backwards, Category Fluency, Phonemic (F-A-S) Fluency Tasks, Boston Naming Test, Visual Search and Attention Test (VSAT), Trail Making Test (A and B), and the Digit Symbol Test. These tests were selected in consultation with neuropsychological experts to reflect domains considered vulnerable to the impact of delirium. Neuropsychological tests are administered at baseline and at 1, 2, and every 6 months thereafter up to 18-36 months. The 1 and 2 month assessments are conducted to evaluate learning or retest effects. Two closely spaced repeat administrations are completed to evaluate for a potential delayed retest effect associated with delirium. The Wechsler Test of Adult Reading (WTAR) is administered once at baseline as a measure of pre-morbid intelligence (Table 4). 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.

The GCP has excellent psychometric properties with minimal ceiling and floor effects across a broad range of values.⁴¹ While the GCP will be the primary cognitive outcome measure, we will also examine domain-specific effects, looking at both individual neuropsychological tests and combinations of cognitive domains (for example, attention, executive functioning, memory, language). Since the effects of delirium may not be uniform across all domains, these analyses will help to determine if certain aspects of cognitive functioning, such as executive function and attention, are more susceptible to the detrimental long-term effects of delirium than others, such as memory and language.

Physical Functioning—The physical functioning measures for this study include the basic Activities of Daily Living Scale (ADLs),⁴² Instrumental Activities of Daily Living Scale (IADLs),⁴³ and the physical functioning domain of the Short Form Health Survey (SF-12),⁴⁴ at baseline, 1 month, 2 months, 6 months and every 6 months thereafter. The ADL scale assesses the ability to perform 7 basic care skills (feeding, bathing, dressing, grooming, using the toilet, transferring, and walking). The IADL scale assesses the ability to perform 7 complex activities (using the telephone, grocery shopping, using transportation, cooking, housekeeping, taking medications, and handling finances). The SF-12 is a multi-dimensional health outcomes instrument assessing health, social functioning, role-emotional, and physical and mental health; the physical function domain of the SF-12 will be used as a primary study outcome. These variables will be examined individually and as a composite measure.

Secondary Outcomes

Secondary outcomes include general health status (SF-12), re-hospitalization, institutionalization, death, and incident dementia or mild cognitive impairment by clinical consensus (Table 2). Information about re-hospitalization, institutionalization, and death (and cause of death) will be obtained from patient and family interviews and medical record reviews. The time and cause of death will be obtained from medical record review and confirmed with information from the Social Security database and the National Death Index.

Clinical Consensus Panel—Ratings of incident dementia or mild cognitive impairment (MCI) will be made by expert review during regular Clinical Consensus Panel (CCP) meetings. The CCP consists of 7 experienced clinical experts in cognitive assessment, including 1 cognitive neurologist (chair), 2 neuropsychologists, 2 geriatric psychiatrists, and 2 geriatricians. Prior to each quarterly meeting, panel members review all study data from participants scoring 1.5 standard deviations below population means on 2 or more cognitive domains on neuropsychological tests. The data reviewed include age, education, first language, baseline WTAR score, medical diagnoses and medications, presence of CAM features, neuropsychological testing results, patient- and informant-rated versions of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) short-form,⁴⁵ and ADL and IADL scores. MCI and dementia ratings are assigned based on fulfillment of NIA-AA criteria,^{46,47} and with consensus agreement of at least 5 of 7 panel members. The CCP also reviews major intervening events to determine if these may be associated with cognitive decline (e.g., major stroke, head injury) independent of delirium.

Additional Study Variables

Additional variables to be collected for this study are indicated in Table 4. These include key risk factors and co-variables for analyses. Further detail on novel risk factors—plasma biomarkers, imaging markers, and reserve markers—is provided below.

Plasma Biomarkers for Delirium—This project aims to discover plasma biomarkers related to delirium risk,⁴⁸ delirium incidence, and duration utilizing multiplex analysis to describe cytokine and plasma protein “signatures”. Blood is collected from the entire cohort at 4 time points: a) at the time of the baseline study assessment, b) immediately after surgery in the post-anesthesia care unit, c) on postoperative day two, and d) one-month after surgery. The biomarker discovery process will compare specimens of patients who develop delirium during their index hospitalization with those of matched patients who do not. The relationship of the cytokine and protein signatures with long-term cognitive and functional outcomes will also be examined.

Imaging Markers for Delirium—Magnetic resonance imaging (MRI) of the brain will be used to discover risk and disease markers associated with delirium through volumetric, white matter hyperintensity, noncontrast blood flow, diffusion, and diffusion tensor measures. These will be used to characterize the functional and structural effects of delirium in the brain by comparing patients who develop delirium with those who do not.⁴⁹ A subgroup of 150 patients who pass the MRI eligibility screen (i.e., no contraindicated implants or metal fragments in the body, or claustrophobia) are imaged on the same 3 Tesla MRI scanner at baseline before the initial surgery and at least 90 of these are imaged again at 12 months after the surgery. The baseline measure will be used to identify potential imaging risk markers for delirium. The follow-up scans will be used to evaluate for long-term changes associated with the development of delirium.

Reserve Markers for Delirium—This project will examine the role of cognitive and brain reserve, a measure of the resilience of the brain to withstand neuropathological damage, on the occurrence and consequences of delirium.⁵⁰ A multifaceted model for reserve in delirium will be created to determine whether higher reserve is independently associated with a lower rate of incident delirium and less long-term cognitive and functional decline. Incorporating a life course perspective, reserve markers include education and occupation (self and parental), lifetime cognitive activities, physical and social activities, pre-morbid intelligence, head circumference, and brain volume.

Research Resources—The study data and materials will provide a unique, clinically-detailed, longitudinal resource on older patients undergoing hospitalization and major surgery. Moreover, the bio-repository of genetic material and plasma will be a resource for future investigation, including additional biomarker discovery studies.

Data Management and Analysis

A database management system has been developed to track a participant's status throughout the course of the study, to produce timelines for interviewers, and for continuous quality assessment and progress reports. We use a combination of electronic data capture (EDC) and paper data collection procedures. We use RedCAP⁵¹ or web-based data collection and Pepper Informatics⁵² for local data collection. We use EDC wherever feasible but use paper forms when a written record is desired (e.g., neuropsychological testing) or when we cannot be assured that interviewers will have internet access (e.g., hospital floors, patients' homes).

Data management includes daily integration of EDC and paper forms, email notifications of pending visits and scheduling information, and development of an interim project database for preliminary analyses. According to a schedule determined *a priori* by the data core and approved by our Scientific Advisory Board, we perform periodic data freezes on a sample with verified and cleaned data (i.e., double data entry and consistency checks evaluated and resolved). Frozen data files are used for interim reports, drafting analysis plans and mock tables to address project aims, and preliminary abstracts and manuscripts on study methods. During all preliminary analyses, the analysts and investigators remain blinded to results linked to the main study hypotheses through use of a random, blinded variable for delirium status.

Statistical Considerations—Sample size was determined by balancing many factors. First, we considered feasibility of patient accrual within the planned enrollment period. Second, we wanted to restrict our pool of eligible surgeries to those with a moderate-to-high delirium risk. Being more restrictive produces a more homogeneous patient sample, but limits accrual and generalizability. We also considered our other eligibility criteria, and their impact on feasibility, delirium risk, and statistical power. Each of the four projects has its own aims and hypotheses, some using the entire expected sample and others using a limited subset. We verified adequate sample size to test each hypothesis with calculations based on pilot data or previously published studies. We determined that a sample of 550 patients, with an anticipated incidence of postoperative delirium of 25%, would be adequate to address the needs of the aims of all 4 projects. In addition, we are recruiting a sample of 120 non-surgical participants from primary care clinics at BIDMC who will provide normative data on neuropsychological test performance and the impact of retest effects on estimated test scores.

Study Management

The Program Project supports the 4 study projects with 3 research cores: Administrative, Epidemiology, and Data Cores. Well-coordinated meetings are held between all Cores and Projects for ongoing scientific exchange and procedural clarification. The Administrative Core meets weekly to provide overall leadership for the project, assure adherence to study timelines, complete required progress reports, and address all institutional review and human subjects compliance issues. The Epidemiology Core leaders and staff hold weekly meetings to address questions from the field team (coding, participant issues, and scheduling). The Data Management and Analysis Core leaders and staff meet weekly to discuss ongoing data tracking, quality, and analysis issues. In addition, specific project analysis meetings are held on a bimonthly basis to advance the primary aims of each project.

Executive Committee—The Executive Committee, the main decision-making group for the program project, consisting of all project and core leaders, clinical experts, and the study project director, meets twice monthly to optimize scientific integration and productivity. Subcommittees of the Executive Committee include the Clinical Consensus Panel to determine incident dementia, the Clinical Adjudication Team to determine initial eligibility (e.g., eligible surgery, exclusionary conditions), the MRI Safety Panel to handle adverse events or unexpected MRI findings, and the Publications and Ancillary Study Committee for publication and data use oversight.

Operations Committee—Study policies, operations, and management issues are addressed during weekly operation meetings attended by all core leaders, co-leaders, and project directors. A detailed Operations and Procedures Manual was developed during study initiation and is regularly updated with decisions made at these meetings. The manual and updates (indexed by date and topic) are posted on a password-protected study website, accessible to all study investigators and staff.

Other Administrative Elements—A Scientific Advisory Board consisting of 6 external interdisciplinary experts (anesthesiology, cognitive neuroscience-reserve, geriatric medicine, geriatric nursing, pulmonary medicine-biomarkers, and radiology), 5 internal experts, and an NIH representative meets yearly to provide independent scientific review, monitor progress, and provide ongoing direction and input for the study investigators. Meetings with the Safety Officer are held semiannually to ensure the protection of human subjects. All adverse events and deviations are reported to the Safety Officer and IRB on a regular basis. The Fiscal Management Committee meets monthly to ensure fiscal accountability and budget tracking.

DISCUSSION

Over two decades of delirium research have improved our ability to diagnose this common and serious disorder. Previous studies have also identified strategies for decreasing the incidence and impact of delirium for certain patient populations. Nevertheless, the toll that delirium takes on older patients, and on healthcare spending, remains unacceptably high. Delirium takes its toll not only during the acute episode of delirium but, in many patients, through long-term cognitive morbidity following the episode. Without further advances in the prediction, prevention, and treatment of delirium, this toll will only increase as the population of those most at risk, the elderly, continues to grow. Advances in clinical management can only come with a better understanding of the biology and outcomes of delirium.

Recent technological advances in biomarker identification and neuroimaging offer new pathways for the discovery of the biological underpinnings of delirium. Refinements in delirium and dementia assessments have improved our ability to screen, quantify, and track delirium and dementia. Theories of brain and cognitive reserve have opened new avenues of research for interventions that might attenuate delirium and dementia. For the first time, this program project brings these advancements “under one roof” to study in a prospective, coordinated, and interdisciplinary fashion the risk factors, biological markers, reserve markers, and long term effects of delirium. This synergistic and coordinated interdisciplinary effort truly leads to a “whole that is greater than the sum of its parts”. However, the logistical challenges inherent to running a large multi-project program of this nature are formidable, and this manuscript describes our response to addressing these challenges.

The benefit of running inter-linked studies of this nature, in addition to cost-effectiveness, is the opportunity to research a complex, multifactorial clinical syndrome in a prospective manner along multiple investigative fronts. Importantly, the program project also includes the creation of a biorepository of data, images, plasma, and genetic materials for future research. Moreover, the rigorous and innovative approach to address a common, complex, multifactorial clinical syndrome may be applicable across a diverse array of clinical conditions.

Methodological Considerations

In designing the program project, the investigators grappled with several key issues that may be informative to others designing similar studies or to the general audience interpreting study findings. These are described below:

1) Inclusion of Patients with Unrecognized Dementia or MCI—While we always intended to exclude patients with clinically recognized dementia, we carefully considered whether or not to use the detailed neuropsychological testing and proxy interviews in our baseline assessment to exclude patients with more subtle dementia or mild cognitive impairment. The primary motivation for exclusion would be to have a “pure sample” without pre-existing cognitive disorders that might confound the relationship between delirium and long-term outcomes. However, since the vast majority of older patients undergoing surgery do not undergo such detailed neuropsychological testing, our study sample would be highly selected and findings would not be generalizable to any clinical population. Ultimately, we decided to include such patients, and to increase our sample size from the initially planned 500 to 550 so that we could conduct sensitivity analyses to determine whether or not the final study conclusions differ whether we include or exclude patients with mild dementia or MCI.

2) Breadth of Surgical Procedures—A second decision that we carefully considered was the breadth of surgical procedures to include in our study. We excluded cardiac surgery (because of potential issues with cardiopulmonary bypass), surgeries with high mortality rate (e.g. pancreatic cancer resection) and urgent/emergency procedures where we would be unable to measure the patient’s pre-surgical baseline (e.g. hip fracture repair). Among the remaining non-cardiac procedures, we focused on major surgical procedures commonly performed in older adults with a hospital length of stay of at least 2 days, and with a moderate to high delirium risk (overall 25%). Including the broadest selection of such procedures would benefit the epidemiological studies (Projects 1, 4), while using a very narrow set of procedures would benefit mechanistic studies (Projects 2, 3). In the end, we chose a compromise position, in which we are enrolling seven major types of surgery: total hip replacement, total knee replacement, lumbar laminectomy, cervical laminectomy, lower extremity vascular bypass surgery, open aortic aneurysm repair, and colectomy (open or laparoscopic). This more limited set of surgical procedures captures approximately 50% of the older surgical population, but still enables us to adjust for, stratify on, or match by surgical procedure, as is being done in Project 2. We carefully considered new minimally invasive surgical procedures, so that some surgeries (laparoscopic colectomy) are eligible since these patients stay as long as their open counterparts, while others (endovascular aortic aneurysm repair) are not since these patients typically stay only 1-2 days in the hospital.

3) Isolating Effects of Delirium—Finally, we carefully considered how to separate out delirium effects from the complex perioperative milieu. Although randomized trials are considered the “gold standard” for assessing causality, it would be impossible to randomize patients to delirium or no delirium groups. Despite being observational, we believe that our study incorporates key elements that represent a significant advance over the existing

literature. These include: 1) carefully characterized baseline status of all participants, 2) detailed intraoperative and postoperative follow-up including daily hospital interviews and medical record review, 3) in-depth longitudinal follow-up with patient and proxy interviews, medical record review, and careful ascertainment of intercurrent events, and 4) incorporation of a non-surgical comparison group. These elements will enable us to use sophisticated longitudinal analytic techniques with careful adjustment for confounders of long term outcomes, thus enabling us to mount the most sophisticated effort to date to attribute such outcomes to delirium.

CONCLUSION

This program project 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. Identification of cogent biomarkers, imaging, or reserve markers for delirium risk may help us target high-risk patients preoperatively—for instance with new anesthetic strategies to minimize delirium—or to follow the response of delirium to treatment strategies. The study of cognitive reserve may help us to identify reserve-enhancing educational, behavioral, or lifestyle strategies that can reduce the risk of delirium.

While we cannot anticipate our specific findings, our study's broad hypotheses are that delirium itself may be a major initiating or predisposing factor for long-term cognitive and functional decline, and that patient- and hospitalization-specific factors are major determinants of the incidence of delirium. If these hypotheses are supported, then our findings would necessitate a marked shift in how delirium is addressed clinically. In fact, delirium would need to be handled as a true medical emergency in all cases, with timely interventions for recognition and treatment to prevent progressive cognitive and functional decline and related adverse outcomes. Heightened efforts to recognize delirium would be required, along with changes in clinical management, including stopping the common practice of discharging patients from the hospital who are actively delirious.⁵³

The consequences of these potential shifts in clinical care are substantial. With prevention of 30-40% of delirium cases—which may be achievable based on previous work—there is a promise of dramatic preservation of long-term cognitive health in our growing older population. This will offer substantial benefits to the health of our nation's seniors, to the healthcare system and to society at large, with a potential savings of over \$60 billion per year.⁷

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Abbreviations

BIDMC Beth Israel Deaconess Medical Center

BWH	Brigham and Women's Hospital
HMS	Harvard Medical School
BU	Boston University School of Public Health
HSL	Hebrew SeniorLife
MGH	Massachusetts General Hospital
PI	principal investigator
UCONN	University of Connecticut Health Center

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1. . Conceptual Model for Primary Study Aims

Table 1**Inclusion and Exclusion Criteria**

Inclusion criteria	Screening procedure
• Age 70 years or older	Medical record
• English speaking (English need not be first language)	Medical record or recruitment telephone call
• Scheduled for eligible high-risk surgery: • Orthopedic (total hip or knee replacement; lumbar, cervical or sacral laminectomy) • Vascular (lower extremity arterial bypass surgery; open abdominal aortic aneurysm repair; lower extremity amputation) • General (open or laparoscopic colectomy)	Medical record
• Planned general or regional anesthesia	Medical record
• Scheduled at least 6 days prior to surgery to allow adequate time for the baseline assessment	Medical record
• Planned admission to the hospital for at least 2 days	Medical record
• Living within 40 miles from study hospitals	Medical record
Exclusion criteria	
• Active delirium	Medical record, recruitment telephone call, or baseline cognitive assessment
• Dementia (dementia diagnosis or score <69 or education-adjusted equivalent on baseline 3MS cognitive test)	Medical record, recruitment telephone call, or baseline interview
• Hospitalization within 3 months prior to enrollment to minimize risk of recent delirium	Medical record
• Terminal condition with life expectancy < 6 months (e.g., metastatic cancer, pancreatic cancer, or receiving palliative care)	Medical record
• Inability to perform cognitive tests due to legal blindness or severe deafness	Medical record, recruitment telephone call, or baseline interview
• History of schizophrenia or psychosis	Medical record
• Current chemotherapy due to patient time burden	Medical record
• Documented history of alcohol abuse or withdrawal within last 6 months and/or reporting more than 5 (4) drinks per day for men (women)	Medical record or baseline interview
• Unable to pass assessment for capacity to provide informed consent	Baseline interview

Table 2

Schedule of Delirium and Outcome Assessments

Assessments	Baseline	Hospital	Months: 1	2	6-36
<u>Delirium</u>					
● Confusion Assessment Method (CAM)	X	X	X	X	X
● Memorial Delirium Assessment Scale (MDAS)	X	X	X	X	X
● Delirium Symptom Interview (DSI)		X	X	X	X
● Delirium duration, persistence, and recurrence		X	X	X	X
● Family Confusion Assessment Method	X		X	X	X
● Chart Review Method		X			
<u>Primary Outcomes</u>					
● Cognitive Function: General Cognitive Performance Measure [composite neuropsychological measure]	X		X	X	X
● Physical Function					
○ Activities of Daily Living	X		X	X	X
○ Instrumental Activities of Daily Living	X		X	X	X
○ Physical Functioning Component (SF 12)	X		X	X	X
<u>Secondary Outcomes</u>					
● Incident Mild Cognitive Impairment or Dementia	X		X	X	X
● General Health Status (SF 12)	X		X	X	X
● Rehospitalization	X	X	X	X	X
● Institutionalization	X	X	X	X	X
● Death, Cause of Death		X	X	X	X

Table 3**SAGES Neuropsychological Test Battery**

Test	Description	Domain(s) Tested
Visual Search & Attention Test (VSAT) ⁵⁴	Four timed visual cancellation tasks where the participant must cross out letters and symbols that are identical to a target.	Executive, visuospatial function
Hopkins Verbal Learning Test, Revised (HVLt-R) ⁵⁵	A list of words is read to the participant, who is asked to repeat the list back over multiple learning and delayed recall trials.	Verbal episodic memory
WAIS Digit Span Forward and Backward ⁵⁶	Participants are asked to repeat a string of digits forward and in reverse order.	Attention
Category Fluency ⁵⁷	The participant must generate as many words as possible from a semantic category (e.g., "animals").	Executive function, semantic memory, language
Phonemic Fluency Tasks ⁵⁸	The participant must generate as many words as possible beginning with a given letter over three trials (e.g. "F", "A", and "S").	Executive function, semantic memory, language
Boston Naming Test ⁵⁹	The participant is presented with drawings of common objects, which then must be named correctly.	Confrontation naming, language
RBANS Digit Symbol Test ⁶⁰	Using a key provided, the participant matches symbols to numbers as quickly as possible while being timed.	Executive function, visuospatial function
DKEFS Trail Making Test ⁶¹	The participant must connect a sequence of alternating numbers and letters.	Executive function, visuospatial function

HVLt-R=Hopkins Verbal Learning Test-Revised; WAIS=Wechsler Adult Intelligence Scale; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; DKEFS=Delis-Kaplan Executive Function Scale; WTAR=Wechsler Test of Adult Reading

Table 4

Additional Study Variables

Variable/Instrument	Source of Information
<u>Patient and General Descriptors:</u>	
● Demographics	INT, MR
● Education	INT
● Surgical type	MR
<u>Cognitive function:</u>	
● Neuropsychological test battery (see Table 3)	INT
● 3MS ³³	INT
● Brief cognitive screen	INT
● Digit span test ⁶²	INT
● Premorbid intelligence, WTAR ⁶³	INT
● Cognitive reserve markers ⁵⁰	INT
● IQ Code short version ⁴⁵	INT, FAM
<u>Delirium-related factors:</u>	
● Anesthesia type and duration	MR
● Specific Activities Scale (SAS) Class	INT
● Abnormal labs (Na, K, Glu, Hct)	MR
● Vision impairment, Jaeger test ⁶⁴	INT
● Hearing impairment, Whisper test ⁶⁵	INT
● BUN/Cr ratio 18 ⁶⁶	MR, LAB
● Precipitating factors ⁶⁷	INT, MR
● Intercurrent illnesses ⁶⁷	INT, MR
● Intra- and post-operative complications	MR
● Poor nutrition (Body Mass Index, weight loss, Alb)	INT;MR
● Brief Pain Inventory ⁶⁸	INT
<u>Illness-related factors:</u>	
● Medical diagnoses	MR
● APACHE II score ⁶⁹	MR
● Charlson comorbidity score ⁷⁰	MR
● Medications	MR
● Health habits (alcohol, smoking)	INT, MR
● Vascular risk factors (smoking, HTN, DM, chol, VD)	INT, MR
● Hospital (index) length of stay	MR
● Inter-current illnesses	INT, MR
● Depression (GDS-short form) ⁷¹	INT
<u>Biomarkers:</u>	
● Cytokines	LAB

Variable/Instrument	Source of Information
● APOE -ε4 allele	LAB
● Proteomics	LAB
● Neuroimaging markers (cortical volume, flow)	MRI

Cognitive reserve markers include: education, occupation, income, wealth, head circumference, Cognitive Activities Scale, WHI Activities Scale; EPESE Activities. 3MS=Modified MMSE; WTAR= Wechsler Test of Adult Reading; 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; GDS=Geriatric Depression Scale; INT= patient interview; MR= medical record abstraction; FAM=family/caregiver interview; LAB=blood testing;