

MANUAL OF PROCEDURES

Perioperative Cognitive Protection - Dexmedetomidine and Cognitive Reserve

“Dexlirium Trial”

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Title of Study	Perioperative Cognitive Protection - Dexmedetomidine and Cognitive Reserve
Investigator/Study Centers	The trial will be conducted in the United States at approximately 7 clinical sites. The coordinating center for the trial will be at the Mount Sinai School of Medicine and the Data Management Center will be at the Cleveland Clinic.
Phase of Development	Phase III/IV
Objectives	<p>Specific Aim I: To test the influence of dexmedetomidine as compared to placebo on the occurrence of PD in an elderly general surgical population of patients.</p> <p>Specific Aim II: To test the influence of dexmedetomidine as compared to placebo on the extent of scores on cognitive measures previously used to index POCD between preoperative value and 3 and 6-month follow-up retests in that same population.</p> <p>The Secondary Aim of this study is: Secondary Aim: To establish the role of preexisting cognitive impairment in the development of PD and/or POCD</p>
Design	This is a randomized double blinded, parallel group, placebo-controlled study of the effects of perioperative dexmedetomidine on the incidence of postoperative delirium and postoperative cognitive dysfunction.
Planned Sample Size	It is anticipated that 706 patients will be randomly assigned to 1 of two treatment groups (placebo or dexmedetomidine 0.5 ug/kg/hr) with 303 patients in each group.
Patient Selection	<p>Inclusion Criteria</p> <ul style="list-style-type: none"> • 68 and older • elective major surgery under general anesthesia(major surgery is defined by a planned 2 day hospitalization) • ASA physical status I-III • capable and willing to consent • MMSE \geq 20 (to exclude dementia) <p>Exclusion Criteria</p> <ul style="list-style-type: none"> • Cardiac surgery • Intracranial Surgery • Emergency Surgery • Planned postoperative intubation • Patients with severe visual or auditory disorder/handicaps • Illiteracy • Patients with clinically significant Parkinson's Disease • Patients not expected to be able to complete the 3 and 6 month postoperative tests • Patients on dialysis • Sick sinus syndrome without pacemaker • Hypersensitivity to drug or class • Current 2nd or 3rd degree AV block • History of clinically significant bradycardia • Contraindication to the use of an α2A-agonist • Presence of a major psychiatric condition such as bipolar disorder, major depression, schizophrenia, or dementia • ASA physical status IV or V • Noticeable Hepatic Dysfunction
Main Efficacy Parameters	<p>The primary measure will be the incidence of delirium in the immediate postoperative period as measured by the delirium battery.</p> <p>Secondary parameters will be derived from the cognitive testing values obtained before and after surgery. An incidence of POCD for both groups will be determined.</p>

2. Introduction

Postoperative Delirium (PD) and Postoperative Cognitive Dysfunction (POCD) are syndromes of central nervous system (CNS) dysfunction that significantly complicate the recovery of a proportion of elderly patients following surgery. In 2004, 7.9 million patients over the age of 65 underwent a surgical procedure¹ with an estimated 5-40% of all of these patients subsequently experiencing either PD or POCD.²⁻⁴ There are no approved therapies for either disorder.

The proposed trial builds on extensive prior work characterizing PD and POCD. Delirium is typically a transient syndrome characterized by a de-novo appearance of several pathognomonic behaviors, including disorientation, decreased attention span, sensory misperceptions, a waxing-and-waning type of confusion, and disorganized thinking. PD typically occurs on postoperative days 1-3 and is associated with prolonged hospital stays, increased risks for morbidity and mortality and significant health care expenditures.^{5,6} In a recent study, of length of stay for surgical patients with delirium was 6.0 days, as compared to 4.6 for patients that did not develop delirium.⁷ The average additional cost per delirious surgical patient was \$2947,⁷ which translates into more than \$2 billion additional health care dollars per year, in the United States. POCD is a developing concept characterized by persistent deterioration of cognitive performance defined by pre and post-operative cognitive testing. POCD is not a normative experience, with only about 10% of elderly patients having measurable decline at 3 months, depending on the severity criteria employed.⁸ POCD can be clinically significant and impair activities of daily living.⁸

The etiologies of both PD and POCD remain unknown. Controversy exists over whether delirium is a marker or risk factor for subsequent persistent cognitive impairment⁹. There is, however, little doubt that delirium may precede subsequent cognitive impairment. PD and POCD have been primarily evaluated in different studies by different groups of investigators, such that studies of PD tend to use relatively unsophisticated measures of long-term cognitive function, and vice versa. Nonetheless, there are numerous areas of overlap between the predictors and putative causal mechanisms for both entities. Major, but not minor surgery is a significant precipitant of PD and POCD (See Prelim Data). Anesthesia, analgesia and sedation all utilize medications that might be implicated in the development of CNS dysfunction, however radically different anesthetic techniques (regional vs. general anesthesia) do not alter the incidence of delirium or POCD.¹⁰⁻¹² The neuroendocrine stress response to surgery, including the immediate postoperative period, remains an important potential etiologic factor. In particular, our data suggests that stress in the immediate postoperative period is poorly controlled by all anesthetic techniques and the normal diurnal variation in cortisol is suppressed in subjects who develop POCD.¹³

α_{2A} -adrenergic agonists blunt the neuroendocrine response to surgery with regard to cortisol, β -endorphins, arginine vasopressin, epinephrine and norepinephrine.^{14;15} α_{2A} -agonists improve neurologic and histopathologic lesions after cerebral ischemia.¹⁶ Dexmedetomidine is a highly selective α_{2A} -agonist currently approved for sedation in the ICU. Dexmedetomidine produces analgesia, sympatholysis, and a light sedation characterized by easy arousal. In one randomized trial of dexmedetomidine, delirium was decreased from a prevalence rate of 50% in patients receiving midazolam or propofol to a 3% rate in patients receiving dexmedetomidine.¹⁷ A particularly interesting aspect of α_{2A} -agonist pharmacology is that its action converges on the endogenous

substrates for natural sleep to produce their sedative action, an effect that could prove beneficial to elderly postoperative patients.¹⁸

We hypothesize that treatment with dexmedetomidine will diminish both PD and POCD. The essential proposition is that modulation of perioperative stress can ameliorate perioperative delirium and cognitive dysfunction. Our immediate objective is to evaluate, with a randomized clinical trial, the impact of perioperative dexmedetomidine compared to standard perioperative management, on cognitive function in elders undergoing elective major surgery. Seven hundred and six eligible patients 68 years and older will be randomized to receive either a dexmedetomidine or placebo infusion starting prior to an elective operation and extending through two hours postoperative, while patients are still in the PACU. Participants will undergo preoperative assessment of cognitive function, have extensive in-hospital follow-up with repeat cognitive testing at 3 and 6 months following surgery.

Based on both the concept of cognitive reserve as well as clinical experience, there is concern that patients with preoperative cognitive impairment are particularly vulnerable to POCD. In general, such patients have been excluded from previous studies. This study is unique in that we will assess all participants for mild cognitive impairment (MCI) prior to surgery. Assessment of the impact of preexisting cognitive impairment is a secondary aim. A broad goal of this interdisciplinary project is to evaluate POCD, which is primarily an anesthesia concept, in the more general context of dementing illness as explored by geriatric psychiatry.

2.1. Background

2.1.1. Healthcare Burden of Elder Surgical Care

The number of patients over the age of 65 years who undergo non-cardiac surgery will increase from over 7 million to 14 million over the next three decades.¹⁹ Seventy years ago, surgery was considered a desperate measure for patients greater than 50 years of age, who were thought to be incapable of sustaining the rigors of even an inguinal hernia repair.²⁰ Advances in anesthesia during the last century have allowed surgeons to develop an extraordinary array of procedures with excellent outcomes in an increasingly aged population. Nonetheless, morbidity, mortality, and recovery times for elderly patients are substantially greater than those for younger patients.²¹ Morbidities such as postoperative delirium and cognitive dysfunction appear to predominantly affect elderly patients. This has led to an evolution in both the lay public and health care professionals in which concerns about mortality are being replaced by concerns for cognitive function and health related quality of life following surgery and anesthesia.²² The existing data regarding PD and POCD, developed to a large extent by the current investigative team, have profound implications for initiatives to control length of hospital stay, improve recovery, reduce caregiver burden, better utilize resources, and reduce costs of care. This application was developed in response to recommendations from the recently published Agenda for Geriatric Research for the Surgical Specialties²³ and from the National Research Council report entitled “The Aging Mind: Opportunities in Cognitive Research”.²⁴

2.1.2. Definitions of Major Variables (Also see Methods)

The literature regarding postoperative delirium is confusing – some reports even consider delirium and postoperative cognitive dysfunction as synonymous.²⁵ Disordered hyperactive behavior that occurs during emergence from anesthesia is called emergence delirium and is seen primarily in children, although it appears at all ages.²⁶ Following a relatively calm period, elderly patients may

develop a syndrome referred to as interval delirium or postoperative delirium, which is the phenomenon of principle interest to the investigators.²⁷ Delirium may be described as hyperactive or hypoactive. The term ICU psychosis was a “diagnosis of exclusion”. Current researchers in the area utilize the term ICU delirium and employ CAM-ICU as a diagnostic tool.²⁸ Delirium has been described in medical patients, general and cardiac surgical patients.

Postoperative Delirium (PD) – will be defined in this study by criterion for Delirium presented in the Diagnostic and Statistical Manual for Mental Disorders, 4th edition.²⁹ Assessment of the presence of delirium will be performed with the Confusion Assessment Method³⁰ as applied on postoperative days in the hospital.

Postoperative Cognitive Dysfunction (POCD) – will be defined by specific deterioration on individual tests previously found to be sensitive to deterioration in the postoperative period. Unlike delirium, which is a DSM IVR diagnosis, POCD, as described in our preliminary data, is an emerging scientific construct. There is little data to determine whether POCD is a valid syndromal entity and we have chosen instead to define POCD as deterioration in performance on tests of cognitive abilities that are known to decline in some proportion of patients following surgery. Our initial, quasi-syndromal, definition employed in our preliminary studies required a decline of two standard deviations relative to baseline performance (as indexed by the performance of an extensive normative sample of healthy controls) to be defined as meeting criteria for POCD. Patients with MCI could have significant deterioration but not be able to score two SDs below their baseline performance because of floor effects on the assessment measures, particularly in the area of episodic memory. Thus, in order to more broadly assess POCD, avoiding premature definitions of a “syndrome” and to potentially detect deterioration in MCI patients, we will evaluate the process of deterioration on individual tests as described more extensively in the methods.

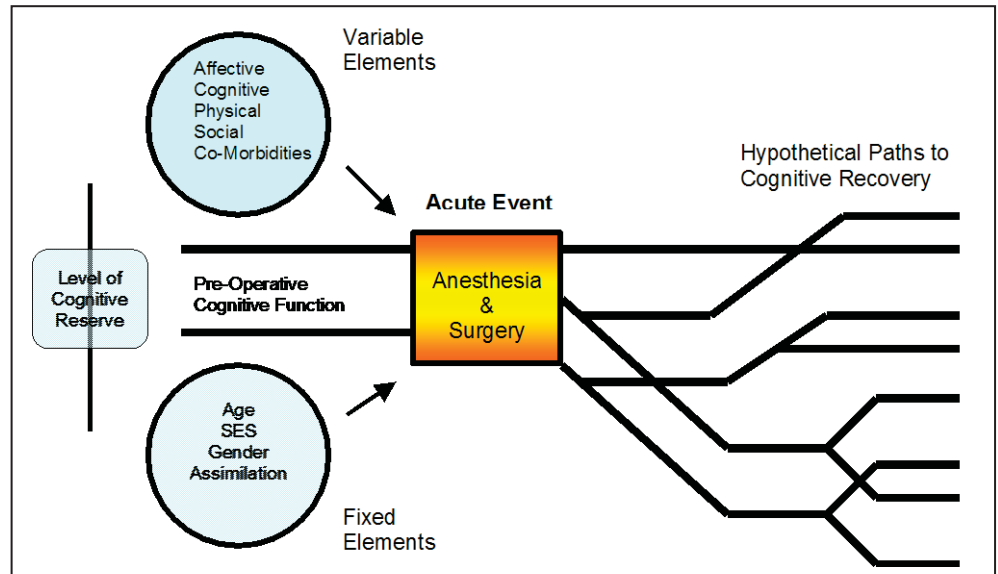
Mild Cognitive Impairment (MCI) - The presence of cognitive impairment short of dementia has been recognized with several different labels. Mild cognitive impairment (MCI) describes a potential transitional zone between the cognitive changes of normal aging and the very earliest clinical features of Alzheimer's disease.³¹ Although not without controversy, MCI has been described in a comprehensive consensus statement of an international working group.³² Petersen³³ provided a formal assessment procedure for detection of amnesic MCI that combines clinical assessment with the systematic use of neuropsychological test data to reliably define the presence of MCI. Additionally the Alzheimer Disease Centers have recently provided a standardized clinical assessment, known as the Unified Data Set (UDS) of cognitive impairment providing data on over 3000 subjects.³⁴ Classifications for MCI were made for amnesic and non-amnesic, single and multiple domain. In addition it identified a smaller category labeled “Cognitive impairment, not MCI. In this submission we will attend to the breadth of the possible cognitive impairment categories. Nevertheless, amnesic MCI remains the most clearly characterized with the most known about its predictive values. The clear operationalization using demographically adjusted norms has been demonstrated in published clinical trials³⁵ and several large multi-center longitudinal studies such the Alzheimer’s Disease Neuroimaging Initiative. We will use the criteria to explore the impact of amnesic MCI on PD and POCD. We intend to implement these criteria at the baseline assessment in order to examine the impact of the presence of all UDS defined categories on PD and POCD. In addition we will take guidance from the UDS for selecting cognitive outcome measures for our assessment of POCD as they reflect a large and relevant database.

Non-cardiac Surgery – In general, PD and POCD are more frequent and more profound following cardiac surgery with cardiopulmonary bypass when compared with non-cardiac surgery; this

is presumably related to cardiopulmonary bypass and/or the nature of the surgical intervention.^{36;37} For this reason, both the literature and the current proposal exclude cardiac surgical patients.

2.1.3. Conceptual Framework

The hallmark of normal aging is declining physiological functional reserve. While basal function may be maintained, the ability to compensate for a variety of stresses is compromised. In the central nervous system, aging results in the loss of cortical gray matter, a reduction in the complexity of neuronal connections, and a decrease in the synthesis of neurotransmitters, coupled with an increase in their postsynaptic degradation. When combined with the effects of age-related



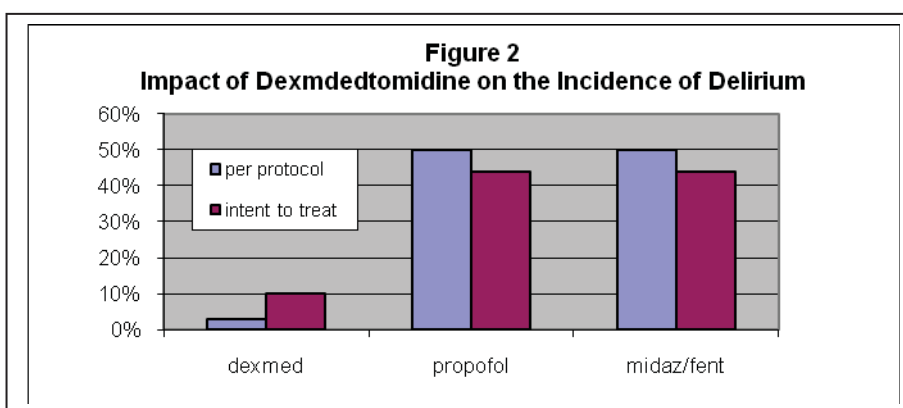
disease, these changes limit the ability of the CNS to respond to the challenges of anesthesia and surgery. Although not strictly a new idea, in 1993 Satz elucidated a theory of brain reserve capacity to explain threshold phenomenon in brain injury, i.e. that a certain amount of brain damage can occur before clinical symptoms appear.³⁸ In a recent review of the intellectual development of what has become known as **cognitive reserve**, Richards and Dreary indicate that there are aspects of brain structure and function that can buffer the effects of neuropathology such that the greater the reserve, the more severe the pathology must be to cause functional impairment.³⁹ Cognitive reserve explains observations of a protective effect of education against the prevalence of Alzheimer's disease,⁴⁰ a phenomenon also noted for POCD.(see preliminary data)

Derived from a theoretical model of functional outcomes following surgery developed for our current grant (Elder Surgery - Functional Recovery Following Beta Blockade 1 RO1 AG18772-01A), we have developed a model of cognitive change following surgery. (See Figure previous page) **A key prediction of this model is that the greater the cognitive reserve, the less likely one is to suffer POCD and/or PD.** A corollary is that patients with cognitive impairment such as MCI are more likely to suffer from POCD and PD. (Additional information regarding cognitive reserve and mild cognitive impairment are included below).

The model defines two types of preexisting factors or determinants: 1) variable elements of function that may be modifiable or amenable to interventions; and 2) relatively fixed elements in the context of cognitive function, which shape function and the roles of the variable elements, but may not be feasible targets for improving recovery. The model focuses on the preparation for, and the conduct and manipulation of, the acute event as a principle determinant of subsequent outcome. Both anesthesiologists and surgeons have made tremendous strides in decreasing the adverse effects of elective surgery. The hypotheses and specific aims of the proposed study are operationalized in accordance with this model. Both the model and the results of the proposed study will direct us towards understanding the course and components of cognitive function following a specific intervention, perioperative dexmedetomidine, in elders undergoing major surgery.

2.1.4. Rationale for using Dexmedetomidine for Preventing PD and POCD

Dexmedetomidine is an α_{2A} -adrenergic agonist which has been positively identified as mediating sedation and hypnosis, analgesia, and sympatholysis,^{41;42} that has been approved for sedation in the ICU. The most compelling reason to believe that dexmedetomidine will prevent delirium is the data reported by Maldonado.¹⁷ In this study, a total of 90 ICU patients following cardiac surgery were randomized to receive dexmedetomidine, propofol, or a combination of fentanyl and midazolam. The delirium was 3% patients receiving dexmedetomidine, for patients propofol, and 50% patients receiving fentanyl/midazolam. An intent-to-treat including patient dropouts still showed a clinically and statistically



incidence of (1/30) for 50% (15/30) receiving (15/30) for (p<0.01). analysis, dropouts still impressive significant

drop (from 44 to 10% - personnel communication). In multiple logistic regression analyses, the postoperative sedation protocol was found to be the most important predictor of delirium, even after adjustment for age, sex, baseline MMSE score, and ASA risk class.

Romero et. al. reported on a series of four patients with delirium associated with agitation and hyperadrenergic states refractory to haloperidol but responsive to dexmedetomidine.⁴³ In addition, although emergence delirium (i.e., delirium after awakening from general anesthesia) in pediatric patients is generally not thought to be the same disorder as postoperative delirium in the elderly, it is intriguing that multiple reports indicate a strong capacity of dexmedetomidine to prevent or ameliorate emergence delirium in children.^{44;45}

There is substantial evidence from animal experimentation that dexmedetomidine produces a neuroprotective effect via the α_{2A} -adrenoceptor subtype.^{46;47} In a rat model of focal cerebral ischemia, the postischemic administration of dexmedetomidine, in a dose that reduces the anesthetic requirements by 50%, had a neuroprotective effect that decreases infarct size by 48% in the cortex.¹⁶ Kuhmonen demonstrated that dexmedetomidine effectively prevents delayed neuronal death in the CA3 area and in the dentate hilus in gerbil hippocampus when the management is started before the onset of ischemia and continued for 48 h after reperfusion.⁴⁸ The exact mechanism(s) by which α_2 -adrenoceptor agonists exert their neuroprotective effect(s) is unknown. At the cellular level, α_2 -adrenoceptor activation has three main effects: (1) inhibition of voltage-operated calcium channels, which are recruited by NMDA-evoked depolarization and contribute to the cytotoxic calcium overload^{49;50}; (2) activation of G protein-linked inward rectifying K⁺ channels, with subsequent neuronal membrane hyperpolarization⁵⁰; and (3) inhibition of adenylate and guanylate cyclase.^{51;52} At supracellular levels, α_2 -adrenoceptor agonists reduce excitatory neurotransmitter release in various experimental models.⁵³⁻⁵⁵ Hoffman et al.^{56;57} showed that dexmedetomidine prevented plasma elevation of epinephrine and norepinephrine, which may in turn aggravate excitotoxicity after cerebral ischemia. Inhibition of ischemia-induced norepinephrine release may be associated with neuroprotection by dexmedetomidine.⁵⁸

Recently, Nelson and colleagues demonstrated that the mechanism for the sedative state produced by the $\alpha 2$ agonists converges on the pathway transducing natural sleep in rats, using expression of c-fos in the locus ceruleus, ventrolateral preoptic nucleus (VPN) and tubomamillary nucleus.⁵⁹ The same investigator provided further proof by way of lesion experiments in the VPN.⁶⁰ Maze and Bonnet noted that “The potential implications of using sedative/hypnotic agents that act through similar mechanisms as natural sleep to induce loss of consciousness are profound. A hypnotic agent that could produce the same reparative changes as natural sleep might speed recovery time in an intensive care setting and counteract the effects of sleep deprivation, a common problem for patients in the intensive care unit and for surgical patients during recovery.”⁶¹ In addition, Nelson suggested that $\alpha 2$ agonists activate sleep pathways to produce more restorative sleep than that induced by downstream modulation of the same pathway by GABA mimetic agents such as benzodiazepines or anesthetic agents.¹⁸

Potential difficulties associated with the use of dexmedetomidine must be considered, particularly when proposing a clinical trial in which the drug will be used differently than the currently approved labeling. Dexmedetomidine is a sedative drug which provides difficulties in blinding study staff and creates specific safety concerns. The research team has some experience with the difficulties associated with proper blinding of operative trials in our current study of intraoperative beta blockade. Dexmedetomidine is known to decrease the need for other anesthetic agents.^{62;63} The approach that we have successfully used is to have the anesthesiologist and the research associates who are doing the cognitive assessments blinded. There will be an unblinded member of the study team (or unblinded site personnel) who will mix the drug and give the study medication to the anesthesiologist doing the case.

These assessments are done at some distance (either before or after surgery), so the effect of the drug is not at all evident or present. The CAM assessment on postoperative day 1 is potentially affected by dexmedetomidine, however, the instrument has been routinely used in the perioperative period in which many drugs with similar effects to dexmedetomidine are routinely used. It is not at all uncommon to arouse a patient from light sleep during postoperative day 1 to undertake the needed assessments. The research coordinator making the assessments will be blinded to group assignment.

Dexmedetomidine, as a sedative drug, has a direct impact on cognitive function. Dexmedetomidine is eliminated exclusively by metabolism and has a $t_{1/2}$ of 1.78 to 2.50 hours in normal volunteers and the harmonic mean terminal half-life of 3.14 hours in ICU patients.⁶⁴ The effects are predictable and time limited to the infusion of the drug. The sedative and cognitive effects of dexmedetomidine are dose-dependent, resulting in a median sedation score of 95 of 100 and slowing of cognitive speed (reaction time, trail-making test) by a factor of about two at the highest plasma concentration.⁶⁵ Normal controls return to baseline at four hours after a dose of 0.6 $\mu\text{g}/\text{kg}/\text{h}$.⁶⁶ Reports of overdose in the literature were associated with over sedation, but no other sequelae.⁶⁷

2.1.5. Current Knowledge Regarding Postoperative Delirium

Delirium, also known as acute confusional state, is typically a transient syndrome characterized by altered consciousness with decreased attention span, changes in cognition or perception not better described by a dementia.⁴ It evolves over hours to days and waxes and wanes over the course of the day. Associated symptoms include sleep-wake and other psychomotor and emotional disturbances.^{68;69} Delirium is distinct from POCD (see below). The onset of PD is most commonly between postoperative days 1-3. It may be sustained for more than a week and is

associated with other medical complications. Delirium has been extensively studied in medical (non-surgical) patients.^{30;70-73} This work leads to clinically relevant predictive models and interventional strategies to modify risk factors and prevent delirium.^{71;74;75} There are at least two reasons why PD may differ from delirium in medical patients.⁷⁶ First, the admission characteristics of the two groups may be different. Nearly all patients hospitalized for medical indications are either acutely ill or have exacerbations of chronic diseases, while most surgical operations are elective and patients have been managed to ensure optimal physical status before entering the hospital. Second, surgery and the associated anesthetics, analgesics and acute pain are generally absent in medical patients, but may contribute to PD. In addition, there appears to be a greater tendency for PD to resolve than delirium patients with medical disease.⁷⁶ The risk factors, strategies to manage risk, treatments, and long-functional consequences of postoperative may differ from delirium in medical patients.

Most cases of postoperative delirium do not have an identifiable etiology, although the range of suspects is frequently legion. Studies aimed at identifying the risk factors for PD have found that increased age, type of surgery, alcohol abuse, certain medications (meperidine and the benzodiazepines), fluid and electrolyte abnormalities, sensory/environmental conditions, infection, and pain increase the likelihood of PD.^{27;77-79} Hypotension and hypoxemia in the perioperative period may⁸⁰ or may not⁸¹ be related to PD. Unfortunately, many of the risk factors associated with delirium are not easily modifiable. Delirium following non-cardiac surgery is associated with increased morbidity and mortality, significantly prolonged hospital stay, delayed rehabilitation, increased risk of nursing home placement, increased costs and decreased functional outcomes.^{5;82-84} (Also see preliminary data) In a large prospective trial in critically ill patients receiving mechanical ventilation, delirium was found to be an independent predictor of prolonged mechanical ventilation, abnormal cognitive status at hospital discharge and a threefold increased risk of death at 6 months.⁸⁵

The pathophysiology of PD remains elusive. Explorations into the role of neurotransmitters and neural pathways associated with delirium and associated behaviors are intriguing, however, at this point they remain primarily speculative.⁸⁶⁻⁸⁹ Many inquiries into this area have examined the role of specific anesthetic techniques or pharmacological agents in PD. The hypothesis driving much of this research has been that drugs administered in the perioperative period aggravate an age-associated central cholinergic insufficiency. Thus far, however, these studies have demonstrated that even profound alterations in anesthetic management have little influence on the incidence of PD. Arguably, the most substantive decision regarding anesthetic management is whether patients should have a regional or general anesthetic. Theoretically, regional anesthetic techniques should be associated with reduced incidence of PD because these techniques minimize exposure to agents that influence central cholinergic activity and drugs associated with delirium in medical patients, such as opiates and benzodiazepines. Further, regional anesthesia deeply depresses the neuroendocrine response to surgery. Unfortunately, multiple clinical studies have failed to find a relationship between the type of anesthesia employed and the development of delirium.^{90;91} A major weakness in previous literature regarding the influence of perioperative management on the incidence of PD is that postoperative management was not controlled. A recent prospective observational study illuminates this issue. (see preliminary data)

Delirium has been diagnosed by a variety of instruments and by clinical observation. Currently, the most widely used instrument is the Confusion Assessment Method (CAM).³⁰ There is a disparate range of incidence rates reported for PD, from 9% to greater than 60%.^{90;92;93} The incidence in patients suffering hip fracture has been the focus of some study, with a 16-62% reported incidence of PD, suggesting that this may be a higher risk subset of patients.⁹³

2.1.6. Current Knowledge Regarding POCD

Many physicians have heard reports of someone who was “never the same” after anesthesia and surgery.^{94;95} Beginning in 1980, a series of small studies suggested that patients undergoing general anesthesia, but not neuraxial anesthesia, were at greater risk for POCD. In a study by Hole of 60 elderly patients (56-84 yrs) undergoing elective total hip arthroplasty, 22.6% of general anesthesia patients experienced POCD, as compared with none of the epidural patients (P<0.01).⁹⁶ Subsequent studies by Chung⁹⁷ in 1987 (n=44) and Tzabar⁹⁸ in 1996 (n=84) had similar findings. In 1995, Williams-Russo presented the first of the adequately powered, prospective, randomized studies of POCD that employed standard neuropsychological instruments.¹¹ This study compared the effect of epidural versus general anesthesia on the incidence of POCD in patients undergoing elective unilateral total knee replacement. Neurocognitive assessment was performed one to seven days preoperatively (n=262), and one week and six months (n=231) postoperatively. Overall, 5% of patients exhibited a decline in cognitive function six months following surgery, but no statistically significant differences were found between the anesthesia groups. In 1998, the first of a series of multi-center studies from the International Study of Postoperative Cognitive Dysfunction (ISPOCD) were published.^{8;99-104} In the first ISPOCD study 25.8% of 1011 patients experienced POCD at one week and 9.9% of 910 patients still had POCD at three months.⁸ The results of these studies are described in the preliminary Data. The relationship between POCD and dementing illness is not at all clear. Studies have indicated that general anesthesia is not a risk factor for Alzheimer’s disease.^{105;106} These retrospective trials had limited power to detect an effect. While it may be reasonable to speculate that POCD is not a major factor in the development of generalized dementia, this remains to be studied in a prospective manner.

The quantitative study of POCD is challenging. The ability to detect, assess the severity of, and characterize POCD depends upon valid assessments of pre- and postoperative cognitive function. The wide variability in normal human cognitive capacities associated with aging and the high incidence of pre-existing mild cognitive impairment in the elderly, make baseline measures a critical component of these evaluations. In the absence of baseline data, it is impossible to attribute poor postoperative test scores to surgical, anesthetic, or illness variables with certainty. Subjective self-reported cognitive symptoms do not substitute for objective cognitive testing, since the poor relationship between the two types of data has been demonstrated repeatedly.¹⁰⁷⁻¹¹² There are significant implications to decisions regarding the degree of deterioration that qualifies as POCD, how that is determined, the role of control groups and the selection of test instruments.¹¹³ The ISPOCD studies (see preliminary data) required a combined 2 standard deviation decline to qualify as POCD. Unlike delirium, POCD is not an established disease. The investigators believe that attempts to define a present/absent “syndromal” definition of POCD are premature, because the field is not yet certain about the exact composition of cognitive deficits that are associated with POCD nor is there agreement on the degree of dysfunction that is clinically significant.^{8;11} Our solution, in the current study, will be to use measures that are shown in our previous study to change significantly, compared to the performance of a healthy non-surgical comparison group, following surgery. While the previous study used a very limited set of tests, we will use other tests that measure the same general cognitive ability (e.g., episodic memory), as well as adding other particularly important cognitive ability areas not assessed in the ISPOCD study, in order to develop a construct validation approach toward the detection of persistent cognitive change. Further, we will use tests that are selected for their particularly strong psychometric characteristics and suitability as outcomes measures in clinical trials.

To date, the etiology of POCD remains unclear. Cerebrovascular disease, cerebral

hypoperfusion, genetic susceptibility and CNS inflammatory phenomenon have all been suggested.¹¹⁴ Although anesthetic technique has not been demonstrated to have significant effects, there are laboratory studies suggesting that general anesthetic agents have toxic effects on CNS anatomy and function.¹¹⁵⁻¹¹⁷ Basic research in both behavioral^{116;118} and neuroanatomical¹¹⁷ animal models may provide important information in the future. A particularly important area of investigation is the search for a biomarker of POCD.^{99;119}

2.1.7. Mild Cognitive Impairment, Cognitive Reserve and POCD

There is a transitional zone in the spectrum of cognitive function from normal aging to degenerative dementias such as Alzheimer's disease.^{31;120} Further study of this concept has recognized memory changes which are thought to be part of normal aging. These have been called age-associated memory impairment (AAMI) and age-associated cognitive decline (AACD).¹²¹ Beyond normal aging, the Canadian Study of Health and Aging used the term 'cognitive impairment no dementia' (CIND) to describe intermediate cognitive function that was not severe enough to be called dementia.¹²¹ The term **mild cognitive impairment (MCI)** is applied to a pathological condition as opposed to a manifestation of normal aging.³² We have adopted Petersen's diagnostic criteria and recommended assessment methods (see methods, sub-section 5) as they are the most developed methods for characterizing the patients we believe to be at increased risk for the development of POCD.^{32;122} In order to distinguish the determination of MCI from our outcomes measures, different assessments are used to define MCI than those used to define POCD.

Cognitive reserve is the hypothesized capacity of the mature adult brain to sustain function in the face of disease or injury when an individual possessing less cognitive reserve would manifest clinical deterioration.¹²³ The hypothesis predicts that older adults with higher cognitive ability will have a lower risk of dementing illness than individuals with less cognitive ability. In addition, the hypothesis suggests that factors associated with higher cognitive ability will also appear to lower the risk of dementia and cognitive changes associated with other stressors such as vascular disease and traumatic brain injury. Adopting this conception, our study design permits us to determine relative impairment based on baseline performance, taking advantage of the specific diagnosis of MCI to classify the risks of patients with limited cognitive reserve. The ability of cognitive reserve to limit PD and POCD may be important prognostic indicators that would alter the enthusiasm for surgical procedures in elderly patients.

Many POCD experts are aware of cases in which individuals suffered severe and enduring cognitive impairment following surgery. Some of these cases are interpreted as pre-existing dementia exacerbated by (or even detected for the first time after) anesthesia and surgery. Unfortunately, these patients typically have not undergone preoperative neuropsychological testing. Patients with mild cognitive impairment have been routinely excluded in most studies of POCD, primarily due to limitations related to the neuropsychological testing of lower functioning patients. In addition, MCI was not a well-developed concept when the original ISPOCD studies were done. Thus, there is very little information available concerning the impact of surgery and anesthesia on many of the patients who appear likely to suffer the worst outcomes. Determination of the relative risk for PD and POCD in patients with MCI will provide important information to patients, their families and their physicians when determining the relative risks and benefits of elective surgery.

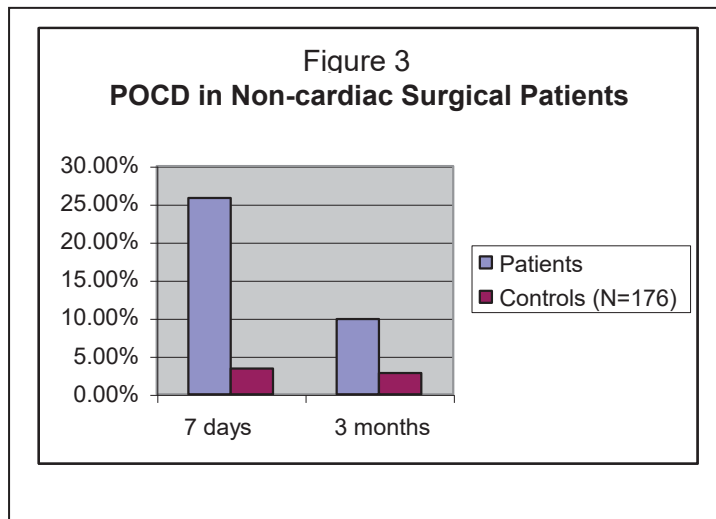
2.2. Preliminary Data

2.2.1. Introduction

The investigative team brings together individuals who have explored POCD, (J.H. Silverstein), postoperative delirium (F. Sieber and C. Jankowski), and cognitive function in psychiatric illness (M. Sano, P. Harvey and A. Reichenberg) to provide a broad background of preliminary data to support the current application. In 1993, Jacob Moller from Copenhagen obtained funding from the European Union under the BIOMED 1 initiative to conduct a large multi-center study, the International Study of POCD (ISPOCD1). A second set of studies was organized under ISPOCD2. Dr. Jeffrey Silverstein was intimately involved in the design, conduct, and multiple publications of both of the ISPOCD programs as the site PI at Mount Sinai in New York. Information from the ISPOCD studies is available at www.sps.ele.tue.nl/ispocd/. The data from the current study will be made available in a similar manner. The ISPOCD collaboration has produced a significant advance in the understanding of POCD following non-cardiac surgery as well as some preliminary data regarding delirium. Dr. Fredeick Sieber from Johns Hopkins and Dr. Christopher Jankowski from the Mayo Clinic have contributed important preliminary data regarding PD.

2.2.2. Characterization of POCD and Role of Ischemia in the Development of POCD

ISPOCD 1 – This is the largest prospective study of cognitive function following non-cardiac surgery. The goals of ISPOCD 1 were to assess the causative roles of hypoxemia and hypotension and the role of age as major risk factors for POCD. Thirteen hospitals in eight European countries and the USA recruited 1218 patients between Nov. 1, 1994 and May 31, 1996. Eligible patients were at least 60 years of age, had for major abdominal, non-cardiac orthopedic surgery under general and had an expected length of days or more. Patients who on the mini-mental state examination¹²⁴ were excluded. completed neuropsychological entry to the study, at discharge hospital or 1 week, whichever was months after surgery. Oxygen was measured by continuous oximetry throughout the night prior during surgery, for the first 24 during nights 2 and 3 following



presented thoracic, or anesthesia, stay of four scored ≤ 23

Arterial blood pressure was measured by automated oscillometry every 3 minutes during surgery, every 15 min in the PACU, and every 30 minutes for the first 24 hours following operation. The psychometric tests were provided in seven languages and were tested for cultural sensitivity.

Patients tests at from the first, and 3 saturation pulse to surgery, hours and surgery.

One hundred and seventy six age matched volunteers from the UK were recruited through advertisements as controls. To ensure that controls were representative of all nationalities, we also recruited 145 national controls, aged at least 60 years, who were partners of patients included in the study or were recruited through advertisement in the same countries as the study centers.

Definition of POCD: We compared changes from baseline in performance of the UK controls at 1 week and 3 months following surgery. The mean change (\pm SD) was calculated and used as an

estimate of retesting effects, which may include both practice effects and simple exposure effects. For each study patient, we compared baseline scores with 1 week and 3 month test results, subtracted the average retesting effect (from UK controls), and divided the result by the control group SD to obtain a Z score for each test. Large positive Z scores indicate deterioration in cognitive function from baseline in patients compared with controls. We also defined a composite Z score from the total of the Z scores for the UK controls, the SD of which was used to normalize the patient's composite Z scores at 1 week and 3 months. **Patients were defined as having POCD when Z scores for two individual tests or the combined Z score was 1.96 or greater.** This definition took into account general deterioration (in all tests) or substantial deterioration in only some tests. In order to compare our previously published experience with the analysis plan proposed for this study, we present the data both as originally published and as reanalyzed in preparation for this proposal.

At 7 days after surgery, we found cognitive dysfunction in 266 (**25.8%** [95% CI 23.1-28.5]) of patients (early POCD). The second postoperative testing was done a median of 99 days after the operation, and we found cognitive dysfunction in 94 (**9.9%** [8.1-12.0]) of patients (late POCD). (See Figure) In the UK control group, 3.4% (1.3-7.3) of participants had scores that showed cognitive dysfunction at 1 week, and 2.8% (0.9-6.5) at 3 months. The national controls did not differ from the UK control group in any of the tests.

Hypoxemia and hypotension occurred frequently. Oxygen saturation of $\leq 80\%$ for more than 2 minutes occurred in 11% of patients and oxygen saturation of $\leq 75\%$ for more than 5 minutes occurred in 4%. Twenty-three percent of patients had a mean arterial blood pressure of 60% or less of reference value before surgery for 30 min or more during or in the first 24 h after surgery. In 7% of patients mean arterial blood pressure was 50% or less of the reference value for 30 minutes or more. There was no relation between different degrees and durations of hypoxemia or hypotension and early or late POCD. *This finding was surprising and suggests that the definitions of hypoxemia and hypotension were too liberal or that mechanisms other than cerebral ischemia and/or hypoxemia cause POCD.*

We found a significant relation between early POCD and increasing age, increasing duration of anesthesia, lower educational levels, second operation, postoperative infections, and respiratory complications. We found significant associations between late POCD (3 months) and increasing age and benzodiazepine usage before surgery. Benzodiazepine use before surgery seemed to have a protective effect against late POCD, but not early POCD.

Table 1
Final Risk Factor Model for Postoperative Delirium

Variable	OR	95% conf.		X ² (df)	p-value
		OR	Int.		
Age	1.09	[1.05;1.13]	(1)	22.42	0.0001
Duration of Anesthesia	1.37	[1.21;1.55]		24.76(1)	0.0001
Type of Operation				27.51(3)	0.0001
Rest (reference)	1				
Upper Abdominal or Thoracic	3.97	[1.56;10.12]			
Lower Abdominal	0.73	[0.19;2.83]			
Orthopedic	1.64	[0.53;5.09]			

ISPOCD 1 represents the largest prospective study of POCD in non-cardiac surgery patients to date. This study clearly defines an important incidence of POCD at 3 months following surgery. POCD was significantly correlated ($p < 0.005$ - Spearman) to Activity of Daily Living score, reflecting both the functional relevance and adverse impact of POCD. However, the study failed to support the hypothesis that POCD was caused by hypotension and/or hypoxemia.

Evaluation of the Sensitivity of the Cognitive Measures: The finding that almost 10% of Lead Center MSSM, Version Date June 28, 2011 Version 1.8

elective surgical patients develop POCD is controversial. Lars Rasmussen from Copenhagen, the lead investigator for ISPOCD2, investigated the impact of variability on the definition of POCD, exploring whether the presence of postoperative cognitive improvement would, in essence, mitigate any POCD.¹²⁵ In this re-analysis, the 3 month test was no longer statistically significant for POCD although the 7 day test remained significant. In this context, the impact of the patients who dropped out before the second test as well as the limited number of patients with MCI in the ISPOCD sample become important.

In order to select the cognitive outcomes for the current study, we examined our previous data on a continuous, as compared to categorical basis. In the ISPOCD study, we designated cases as manifesting POCD if they had declines on either the global score of 1.96 SD or equivalent declines on two of the measures. As noted above, such a categorical decline would not be suitable for use including patients with MCI because of the requirement that these patients already have experienced a decline of 1.5 SD in their performance.

Our analyses the extent to which the five cognitive measures following surgery. We determine whether the differentially sensitive and pattern of changes were consistent with a of decline. In order to declines, we used the scores of the healthy sample and identified the deviation for the change then applied these deviations, correcting for effects, to the change the patients who surgery.

As presented in of the five domains of

functioning manifested relatively consistent patterns of change. For all tests, the proportion of cases that exceeded 1.0 SD in terms of their rate of worsening ranged from 17.4 to 22.2. In the case of the RAVLT variables and digit coding, there was also a rate of worsening that was consistently double the rate of improvements. Thus, when correcting for changes that might be due to random retest error or practice effects, the likelihood of worsening was double the rate of improvement in these three areas, even at 1.0 SD. It is important to note that ISPOCD considered only changes of 2.0 SD consistent with worsening. These data suggest that there is a considerable likelihood of detection of worsening in performance in at least three of these domains at much lower levels of change.

Thus, we conclude that verbal learning and visual-motor speed worsening are detectable following surgical procedures, while interference, and set shifting effects still need to be shown to exceed simple retesting effects. In the current study, we will measure these same domains, using

Table 2:

Proportion of ISPOCD patients experiencing cognitive deterioration at 3 months post surgery by cut off criteria for change in control sample.

Test		1 SD	1.5 SD	2.0 SD
RAVLT Learning	Worsening	18.50	11.60	5.30
	Improvement	8.40	4.20	1.30
RAVLT Recall	Worsening	20.60	11.20	5.10
	Improvement	9.30	5.10	2.40
Digit Coding	Worsening	22.20	8.60	3.70
	Improvement	11.00	3.90	0.70
Stroop (Interference)	Worsening	17.20	10.70	6.90
	Improvement	17.30	11.40	7.70
Concept Shift	Worsening	18.10	10.90	7.00
	Improvement	17.00	9.90	6.30

memory

determined main changed wanted to tests were whether the detected linear pattern identify change comparison standard scores. We standard practice scores for experienced

table 2, three cognitive

other instrumentation that is suitable for multi-site studies. For each domain, we will use more than one measure when feasible, in order to maintain a construct validity approach. Further, we will employ tasks that have previously proven useful in studies of repeated measurement, manifesting high test-retest reliability. Thus, we will also be in the position to determine if there is, in fact, specificity of certain cognitive domains in the realm of POCD following anesthesia and surgery.

2.2.3. Preliminary Data Regarding Postoperative Delirium

Of the 1183 complete cases in the ISPOCD1 database, 99 suffered from postoperative delirium. Of the risk factors considered in this analysis, the final model (see Table 1) included only age, duration of anesthesia and type of operation. Neither hypoxemia, hypotension, ASA status, postoperative pain, benzodiazepine use, N₂O use nor alcohol consumption were significant risk factors for this patient group. Type of operation was dichotomized into upper abdominal or thoracic operations versus all other operations. In this group of patients, there was a significant connection between delirium and four variables that are complications: cardiovascular and respiratory complications, second operation, and death (See Table 3). The confidence intervals surrounding the estimated odds ratios, however, are quite high. The risk of infection does not appear to be related to delirium. There was a statistically significant difference in length of hospital stay between patients having delirium as opposed to those who did not. The odds ratio is 1.50 with a 95% confidence interval of [1.32;1.71]. Patients with delirium had an estimated hospital stay of 14.74 days ([12.91;16.83]) while patients without delirium had an estimated length of stay of 9.78 days ([9.42;10.15]).

An important limitation of this data set is that delirium was determined using DSM III criteria in the absence of a specific instrument such as the CAM. Furthermore, this was not a specific aim of the original project and the data were analyzed retrospectively from the ISPOCD1 dataset. It is likely that many patients with hypoactive delirium were not diagnosed in this group of subjects.

Table 3				
Relationship of Delirium to Postoperative Complications				
Complication	OR	95% conf. Int.	X ²	p-value
Cardiovascular	2.58	[1.48;4.50]	11.14	0.0008
Respiratory	3.08	[1.75;5.41]	15.3	0.0001
Infection	1.43	[0.74;2.78]	1.13	0.2887
Second Operation	6.68	[2.87;15.53]	19.41	0.0001
Death	7.27	[2.33;22.70]	11.66	0.0006

A recent, prospective cohort study, performed by Dr. Jankowski at the Mayo Clinic, examined the predictors and consequences of PD utilizing the CAM. Four hundred twenty-seven elderly patients undergoing elective primary or secondary total hip or knee arthroplasty were enrolled. As part of their preoperative medical evaluation, participants underwent extensive neuropsychological and functional testing before surgery. Tests included the Mini Mental Status Examination (MMSE), the Adult Verbal Learning Test (AVLT), the Stroop Color-Word Test (SCWT), the Controlled Word Association Test (COWAT), the Specific Activity Scale, Activities of Daily Living, Instrumental Activities of Daily Living, the Center for Epidemiological Studies Depression scale, the CAGE questionnaire, the Self-Administered Alcohol Screening Test, and the American National Adult Reading Test (AMNART). In addition to demographic information and past medical history, the particulars of perioperative management were recorded. Presence of delirium was determined daily using the CAM. Patients who developed PD and age-matched, procedure and MMSE-matched controls had repeat neuropsychological and functional testing three months postoperatively.

Forty-six of 427 (10.8%) patients developed PD. There were no differences in verbal

intelligence as measured by the AMNART, level of education, type of operation, depressive symptoms, and level of alcohol use between patients who developed delirium and those who did not. MMSE scores were statistically, but not clinically significantly lower in patients who developed POD. Patients who developed POD had lower age-adjusted preoperative scores on the COWAT (8.4 ± 2.5 vs. 10.0 ± 2.6 , $p=0.0014$), AVLT_{Delayed Recall} ($85.9 \pm 16.1\%$ vs. $95.5 \pm 14.1\%$, $p=0.008$, and, ADLs (11 [7-12] vs. 12 [9-12], $p=0.0003$), than those who did not. These data suggests that MCI may be a predictor of PD.

Regarding intra- and postoperative predictors, continuous peripheral nerve block analgesia was associated with a lower incidence of PD than other forms of pain control (8.1% vs. 19.5% for intravenous patient-controlled analgesia, $p=0.013$). Using stepwise backward elimination analysis, the use of continuous peripheral nerve block analgesia is an independent protective factor against the development of POD (OR 0.30 95% CI 0.141 – 0.646). This finding is important for the proposed study. Perineural infusions of local anesthetics carry the theoretical advantages of regional anesthesia— reduced exposure to CNS active agents and perioperative stress – into the postoperative period. Patients also received supplemental opiates. The incidence of PD in patients with perineural catheters was less than half than in those who received standard patient-controlled parenteral opiates.

These results suggest that modulating the surgical stress response well into the postoperative period may play a significant role in decreasing the occurrence of PD. A limitation of the techniques employed in this study is that they require special expertise and cannot be employed by most anesthesiologists. The intervention in the proposed trial, dexmedetomidine, achieves the same goals as regional anesthetic and analgesic techniques: It modulates surgical stress and decreases the requirement for other agents that are active in the CNS. However, its administration does not require the same degree of specialized expertise as do regional anesthesia and analgesia and it can be utilized in situations where regional anesthesia and analgesia are anatomically impractical.

2.2.4. Minor, less stressful surgery, does not cause POCD

Twelve hospitals in seven countries enrolled patients for this study, using a standardized protocol. Eligible patients were at least 60 years old and scheduled for minor surgery under general anesthesia. Patients were allocated to either in- or out-patient care according to local practice at each hospital. Inpatient surgery was characterized by a maximum expected postoperative stay of 1 night and 1 preoperative night's stay was accepted. Out-patient surgery was characterized by expected discharge from hospital on the day of surgery, with no preoperative night's stay. There were no restrictions on the type of general anesthetics or postoperative analgesia used but intraoperative normocapnia was ensured. The primary outcome of the study was the incidence of POCD (ISPOCD definition), and the protocol included three sessions of neuropsychological testing: one preoperatively, one at approximately 7 days and one 3 months after surgery. Twenty-two of the combined 323 patients undergoing minor surgery displayed POCD (6.8%[4.3–10.1]) 7 days after minor surgery. At 3 months, the incidence of POCD was 6.6%[4.1–10.0]. At 7 days, cognitive dysfunction was found in 16 out of 164 in-patients [9.8% (5.7–15.4)] and in five out of 141 [3.5% (1.4–8.0)] out-patients ($P = 0.033$). In the logistic regression analysis, the following significant risk factors were identified: age greater than 70 years (odds ratio [OR]: 3.8 [1.45–10.1], $P = 0.01$) and in-vs. out-patient surgery (OR: 2.8 [1.05–7.4], $P = 0.04$). There were 34 patients older than 75 years of age in the in-patient group and 32 in the out-patient group. Note that MMSE scores of greater than 24 are often seen in patients with MCI, suggesting that the age effect may be a masked MCI effect because of the increased incidence of MCI with aging. Postoperative cognitive dysfunction was found in six in-

patients (18%[6.8–24.5%]) vs. 0 out-patients ([0–10.9%], $P = 0.01$). After 3 months, no significant difference was found in the POCD incidence between the two groups (8.8%[4.8–14.6] for in-patients and 4.5%[1.8–9.1] for out-patients). No significant risk factor for POCD at that time point was detected in a logistic regression analysis. The incidence of POCD was significantly higher for in-patients when compared with the control group at both 1 week and 3 months ($P = 0.03$ and $P = 0.04$, respectively).

2.2.5. Choice of anesthesia technique and POCD

Twelve hospitals in seven countries contributed patients to the study, each using the same protocol. Four hundred and twenty-eight patients aged 60 years and over for elective major surgery were randomized to receive either regional or general anesthesia between October 1998 and October 2000 with follow-up until March 2001. General anesthesia was performed according to standard institutional practice. Normocapnia was maintained and neuraxial blockade or regional analgesia were not used in these patients. In the regional anesthesia group, spinal or epidural anesthesia was employed and postoperative epidural analgesia was encouraged. Sedation with propofol was permitted at a level compatible with prompt arousal to a verbal stimulus. Cognitive function was assessed using neuropsychological testing methods (see ISPOCD1) preoperatively (baseline) and at 7 days and 3 months postoperatively; comparing the changes between those at baseline with those after surgery. The incidence of POCD at 1 week after general anesthesia was 37/188 (19.7%, [14.3–26.1%]) and after regional anesthesia it was 22/176 (12.5%, [8.0–18.3%]), $P = 0.06$. After 3 months POCD was found in 25/175 (14.3%, [9.5–20.4%]) vs. 23/165 (13.9%, [9.0–20.2%]), $P = 0.93$. This study is the largest published randomized controlled trial of general vs. regional anesthesia and cognitive function. Recently Wu et. al. included this data in their review of this relationship, concluding that there is no difference in the incidence of POCD for regional versus general anesthesia.¹²⁶ Thus, anesthetic drugs per se are probably not the cause of POCD.

3. Study Objectives

The Primary Specific aims of the proposed randomized trial include:

Specific Aim I: To test the influence of dexmedetomidine as compared to placebo on the occurrence of PD in an elderly general surgical population of patients.

Specific Aim II: To test the influence of dexmedetomidine as compared to placebo on the extent of scores on cognitive measures previously used to index POCD between preoperative value and 3 and 6-month follow-up retests in that same population.

The Secondary Aim of this study is to establish the role of preexisting cognitive impairment in the development of PD and/or POCD

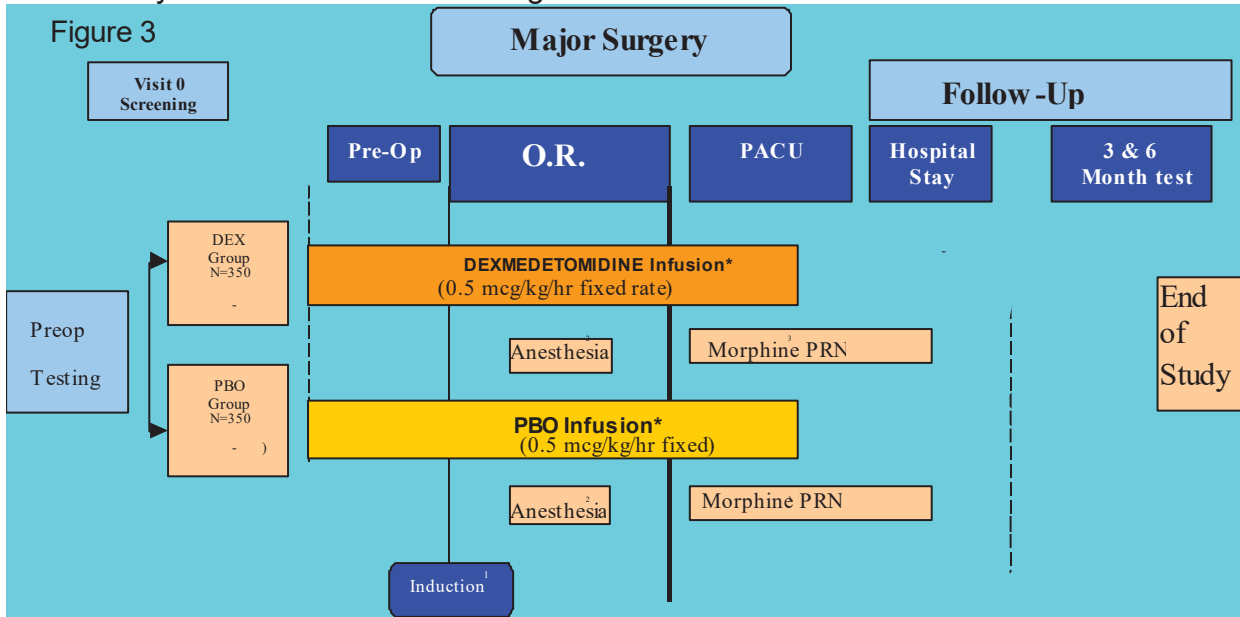
4. Investigational Plan

4.1. Description of Overall Study Design and Plan

Seven hundred and six patients age 68 and over undergoing elective major non-cardiac surgery under general anesthesia will be recruited primarily by participating surgeons. Major surgery is

Manual of Procedures
 Perioperative Cognitive Protection - Dexmedetomidine and Cognitive Reserve

defined as requiring a minimum two day post-operative hospital stay. Participating patients will undergo neuropsychological testing and will donate biological samples before surgery. On the day of surgery patients scheduled to undergo major surgery will be randomized to receive either (1) dexmedetomidine 0.5 mcg/kg/hour or (2) placebo (normal saline administered to match dexmedetomidine rate of infusion). Dexmedetomidine or placebo infusions will begin prior to the surgery (no loading dose), and will be maintained at 0.5 mcg/kg/hour throughout surgery and titrated postoperatively for 2 hours postoperatively. Delirium will be assessed using the Confusion Assessment Method (CAM) on each postoperative hospital day. Follow-up neuropsychological testing will take place at 3 (+/- 6 weeks) and 6 months (+/- 10 weeks) following surgery. The conduct of the study is schematicized in the figure below.



4.1.1. Study Timetable

Table 5 -Study Timetable

Period	9/07-2/08	2/08-9/08	08/09	09/10	10/11	11/12
Finalize Protocol, Data Forms	X					
Train Research Associates/Startup meeting	X					
Develop and test Procedures	X					
Structure Database	X					
Patient Enrollment		X	X	X	X	
Patient Follow-up		X	X	X	X	X
Data Entry		X	X	X	X	X
Perform Quality Assurance		X	X	X	X	X
Data Cleaning		X	X	X	X	X
DSMB Reports			X	X	X	X
Write Reports and Papers				X	X	X

4.2. Selection of Study Population

4.2.1. Inclusion Criteria

- 68 and older
- elective major surgery under general anesthesia (major surgery is defined by a planned 2 day hospitalization)
- ASA physical status I-III
- capable and willing to consent
- MMSE \geq 20 (to exclude dementia)
- Participants literate in English or Spanish

4.2.2. Exclusion Criteria

- Cardiac surgery
- Intracranial Surgery
- Emergency Surgery
- Patients scheduled for ICU admission or planned postoperative intubation
- Patients with severe visual or auditory disorder/handicaps
- Illiteracy
- Patients with clinically significant Parkinson's Disease
- Patients not expected to be able to complete the 3 and 6 month postoperative tests
- Patients on dialysis
- Sick sinus syndrome without pacemaker
- Hypersensitivity to drug or class
- Current 2nd (type II) or 3rd degree AV block
- History of clinically significant bradycardia
- Contraindication to the use of an α_{2A} -agonist
- Current use of α_{2A} -agonist
- Presence of a major psychiatric condition such as bipolar disorder, uncontrolled major depression, schizophrenia, or dementia clinically significant CNS disorder. Stable patients on antidepressant medications are acceptable.
- ASA physical status IV or V
- Noticeable hepatic dysfunction, e.g. twice the normal level * [at the discretion of the investigator]

4.2.3. Recruitment and Informed Consent

The consent process will be undertaken by an individual with appropriate human subjects protection and HIPPA education in the surgeon's office or other appropriate location. Preoperative clinics may also be used when available. Appropriate arrangements for preoperative evaluation for each recruitment site will be determined in advance in order to allow the baseline data to be recorded a minimum 24 hours prior to the elective surgery and a maximum of 30 days. Follow up visits will be coordinated through the surgeon's office.

Each center will be expected to recruit sufficient patients such that two patients complete the protocol each month.

4.3. Administration of Dexmedetomidine

4.3.1. Storage and Handling of Study Drug

The investigational drug for this study is dexmedetomidine HCl (DEX) injection (100 mcg/mL, base). The placebo control is 0.9% sodium chloride for injection prepared in equal volume and to be infused at the same rate and duration as DEX. Hospira will supply the coordinating center with vials for the study infusion. Study medications will be packaged and provided to the site as a bulk shipment every six to twelve months. Additional supplies will be made available to the site if breakage or spillage occurs, or if the subject enrollment warrants additional drug shipment.

The Coordinating Center will supply labels that contain the following information:

- Blinded study drug caution statement
- Protocol Number
- Coordinating Center identification and address

4.3.1.1. Receipt of Study Drug Supplies

This is a double-blind study. Subjects, study personnel and investigators are to be blinded to study drug assignment. The double blinding will be achieved through identical appearance (clear and colorless solution in identical container) and dosing regimen (same infusion volume, rate and duration) for DEX and Placebo. Each site will receive the bulk study drugs and the information for randomization and tracking which are to be stored in a secure location.

4.3.1.2. Storage

The clinical supplies of DEX must be stored at room temperature 25°C (77°F). Excursions are permitted from 15° to 30°C (59-86°F). All clinical supplies (used and unused) must be stored in a secure place until they are dispensed for subject use or are returned to the coordinating center.

4.3.1.3. Return of Study Drug

Instructions for the return or proper disposal of any unused study medication will be distributed to the study sites.

4.3.1.4. Responsibilities

Each Investigator is responsible for the proper management of study drug within the context of each institutions regulations on experimental medications. At a minimum, the study drug must be maintained in a secure area with proper conditions as described above. A medication log will be provided and the investigator must be able to account for every vial of study medication that is dispensed to their site.

4.3.2. Randomization and Blinding

The research team will obtain the randomization assignment by opening the randomization envelopes in the sequence provided. Each envelope will be marked with a site number and patient sequence number. Randomization should take place after completion of preoperative testing session. Patients who are discontinued from study participation prior to randomization will be dropped from the study and no further information will be collected. Patients who are randomized and subsequently dropped from the study will be followed to completion of the 6 month follow-up, to the extent the participant is willing to participate.

4.3.2.1. Un-blinding

In general, the un-blinding of study treatments during a clinical trial is not allowed unless there are compelling medical or safety reasons to break the blinded treatment code (e.g., knowledge of the blinded information is necessary for treatment of SAEs). The Coordinating Center is responsible for the security of the blinded randomization codes for the study. If it becomes necessary to break the blind, the Principal Investigator (PI) or his designee can obtain the randomization assignment from the Pharmacy. The PI or his designee must inform the Coordinating Center that the blind was broken. The NIA and DSMB chair should be notified as soon as possible first by phone, then fax, regarding the necessity of breaking the blinded code. The Principal Investigator may need to notify their IRB, as required. The date and time the blind was broken, and the reason for breaking the blind must be recorded in the source document and entered in the appropriate section of the CRF.

4.3.2.2. Preparation of Study Drug

Study medications will be prepared by appropriate personnel as defined by local regulations. All formulated blinded IV solution bags or syringes are to be clearly marked for the study. Infusion syringe or bag labels will be provided by the Coordinating Center, and may be used by the study site if their operating procedures permit it. The study drug will be diluted to the equivalent concentration of 4 mcg/mL Dexmedetomidine. To prepare this concentration, 1 vial of study medication will be diluted into 48 ml of 0.9% sodium chloride for infusion.

For Example:

- To prepare study drug in 50 mL 0.9% sodium chloride syringe for infusion, utilize one vial of study drug and 48 mL 0.9% sodium chloride
- Shake the syringe gently to mix well.
- Visually inspect bag for particulate matter and discoloration.
- Store this infusion syringe at room temperature for up to 24 hours.

- Write time of expiration on Study Drug label.
 - Study drug (dilute or otherwise) should not be refrigerated.

4.3.3. Parameters for General Anesthesia

Patients enrolled in the study will be scheduled for general anesthesia. Midazolam or other benzodiazepines should be avoided unless specifically needed. The parameters of the general anesthetic are defined only to the extent that induction should be with propofol and maintenance should be Sevoflurane in oxygen/air with fentanyl and the muscle relaxant of choice. Nitrous oxide should not be employed. Thiopental, etomidate and ketamine are acceptable alternative induction agents. When propofol is used for induction of anesthesia, the following are recommended doses:

- 0.5 mg/kg for subject.

Additional propofol may be titrated for induction per the discretion of the anesthesiologist. Sevoflurane will be used to maintain general anesthesia, and the dose will be titrated based on standard of care at the site. Neuromuscular blocking agents may be used for intubation and/or maintenance of anesthesia at the anesthesiologist's discretion.

4.3.3.1. General Monitors in the OR

Vital signs including MAP, HR, SpO₂, end tidal sevoflurane and temperature will be monitored in the operating room and recorded per the time points specified in the case report form. All subjects must undergo continuous SpO₂ monitoring throughout the study drug infusion period.

During the Intra-operative Period, esophageal or other core temperature will be monitored and recorded per the time points specified in the CRF. Abnormal body temperatures are to be recorded as AEs according to the clinical judgment of the Investigator. Subjects with body temperature fluctuations below 35.6°C (96.1°F) or above 38°C (100.4°F) should be evaluated for the presence of an AE.

4.3.3.2. Study Monitors in the Operating Room

Two monitors are included for collecting study specific data. The monitors and disposable probes will be provided to each site. In each case data will be collected from the monitors onto USB memory sticks for transfer to the DCC. Each of the units consigned to the study centers must be brought into each institution in compliance with institutional policies (frequently a no-cost purchase order) and checked and approved by biomedical engineering for use in each institution prior to use in this study.

4.3.3.2.1. Processed EEG

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The BIS Vista Monitoring System (Aspect Systems, Norwood, MA) will be used to measure processed EEG. One unit will be provided to each center. Each center will be supplied with sufficient probes for the expected enrollment. In preparation for each case, the BIS Vista should be plugged in and the time and date should be set to correspond with the time standard for the anesthesia record. (If computerized record, the time on the computer, if hand record, the clock to which the anesthesia team refers.)

Prior to the beginning of anesthesia and prior to the beginning of the study drug infusion one BIS sensor should be applied to the forehead. The monitor should be checked to assure that the sensor check is passed for all four points and that monitoring ensues. Anesthetic titration will be as per standard center procedure.

BIS data should be collected for the entire case. Instructions will be provided to download the data onto a USB data stick. The data will be sent to the DCC on a schedule to be determined. The BIS data will be stored at the DCC and transferred to Aspect Medical Systems. The data transmitted to Aspect Medical Systems will be de-identified.

4.3.3.2.2. Cerebral Oximetry

(NOTE: The cerebral oximetry segment is a substudy under the direction of Dr. Gregory Fischer.)

Cerebral oximetry, based on near infrared spectroscopy (NIRS) technology, provides information on the availability of oxygen in brain tissue at risk during numerous pathological conditions. Cerebral oximetry measures local concentrations of hemoglobin (oxy- and deoxy-), and regional cerebral tissue oxygen saturation (SctO₂) at the microvascular level (arterioles, venules, and capillaries only). As a result, cerebral oximetry SctO₂ is a mixed oxygen saturation parameter which has a value between arterial (SaO₂) and jugular venous oxygen saturation (SjvO₂) under normal physiological conditions, therefore SaO₂ > SctO₂ > SjvO₂. Complementary to the arterial oxygen saturation (SaO₂) measured by pulse oximetry, SctO₂ reflects regional cerebral metabolism and the balance of local cerebral oxygen supply/demand.

The FORE-SIGHT monitor (CAS Medical Systems) was developed with the support of a series of Small Business Innovation Research Grants from the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institute of Health (NIH). It is the only absolute cerebral oximeter cleared by the FDA based on accuracy. The FORE-SIGHT Cerebral Oximeter, with its ability to provide absolute measurement makes it possible to establish threshold values for SctO₂ that can be used to guide clinical interventions.

Each center will be provided with one monitor and sufficient probes to accommodate the expected enrollment. The probes for the cerebral oximeter must be maintained in a secure area. They are costly and cannot be diverted to other use. In preparation for each case, the FORE-SIGHT monitor should be plugged in and the time and date should be set to correspond with the time standard for the anesthesia record. (If computerized record, the time on the computer, if hand record, the clock to which the anesthesia team refers.)

Prior to the beginning of anesthesia and prior to the beginning of the study drug infusion, FORE-SIGHT probes should be applied to the forehead. The monitor should be checked to assure that the sensor check is passed and that monitoring ensues. Once the monitor is assured to be working, the screen of the monitor can be blinded for the remainder of the case. The anesthetic should not be titrated by the SctO₂ measurement.

Cerebral Oximetry data should be collected for the entire case. Instructions will be provided to download the data onto a USB data stick. The data sticks will be sent to the DCC on a schedule to be determined.

4.3.4. Dosage and Administration

Study drug must always be infused using a controlled infusion device that precisely meters the flow of drug, such as a standard intravenous infusion pump system. Manually controlled microdrippers, macrodrippers, or other non-automated infusion devices are not permitted. Study drug must never be rapidly bolused. In order to ensure proper infusion, study drug must never be administered directly into the pulmonary artery.

4.3.4.1. Initiation

Study drug will be infused assuming the concentration of the study drug was 4 mcg/mL. Upon entering the operating room, the infusion will be started at 0.5 mcg/kg/hr. Infusion rate (mL/hr) = weight (kg) x Infusion Dose (0.5mcg/kg/hr)/ Infusion concentration (4 mcg/mL). Example: For a subject of 100 kg, the infusion rate would be $0.125 \times 100 = 12.5$ mL/hr.

The rate of the infusions as well as the start and stop times of the infusions will be recorded in the source document and entered in the appropriate section of the CRF. The Lead Site (Mount Sinai) and the DCC must be notified of any deviations from the protocol-specified doses. The reason for any dose change as well as the start and stop times of the infusions will be recorded in the source document and entered in the appropriate section of the CRF

4.3.4.2. Administration in PACU

Administration of dexmedetomidine will continue for 2 hours in the PACU at 0.5 mcg/kg/hr. As this is a blinded infusion, the strong preference is to maintain the infusion at 0.5 mcg/kg/hr for the entire 2 hours PACU period. It can be decreased or stopped for safety reasons and can be reinstated at the discretion of the investigator. The patient must remain in a monitored setting that includes pulse oximetry until the infusion is discontinued.

Patients should receive a patient controlled analgesia (PCA) pump as soon as they are capable of using the device properly. The settings on the PCA pump will be adjusted to the standard protocol at each center. The amount of morphine infused in the PACU should be recorded. Epidural analgesia is not allowed, however nerve blocks will be permitted.

The blinded medication should be discontinued at 2 hours post-extubation. The patient should be carefully evaluated to be sure that pain is properly controlled prior to discharge from the PACU.

4.3.4.3. Perioperative Events

The most commonly reported adverse events for dexmedetomidine include arrhythmias, bradycardia, hypotension, hypertension, nausea and vomiting. These events will be tracked and recorded in both the OR and the PACU.

4.3.4.4. Temporary Suspension of Study Drug

The investigators should attempt to maintain hemodynamic stability for the patients without altering the study drug infusion. Intravenous fluid and intermittent boluses of pressor agents should be utilized as a first line measure. If, during the active infusion of study drug the supervising clinician decides to suspend the infusion of study, the patients should be evaluated every fifteen minutes with the intention of reinstating study medication within 60 minutes. An example would be a response to rapid blood loss. If the patient remains unstable at the end of 60 minutes, the infusion protocol will be abandoned and the reason for discontinuation will be noted in the CRF.

4.3.4.5. Discontinuation of Study Drug

Subjects will be discontinued from the study if any of the following occurs:

- Clinically significant deterioration of the subject's medical status (per the Investigator's judgment).
- The Investigator believes withdrawal is in the best interest of the subject.
- The subject or subject's legally authorized representative requests withdrawal from the study.
- A selection criterion violation is noted after the subject started study drug

Withdrawal for any reason is considered to be a premature discontinuation. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment. Once study drug has been discontinued, the in-hospital days Follow-up Period begins. The period can last up to 5 days after the procedure has been completed. Randomized subjects who have study drug discontinued due to an AE will have all events documented and followed to resolution. If clinically indicated, a complete laboratory evaluation (chemistry, hematology, and urinalysis) will be performed. Subjects who prematurely discontinue from the study will not be replaced. The date and reason for premature discontinuation of study drug will be recorded in the source document and entered in the appropriate section of the CRF.

4.3.5. Blood Specimens

All centers will be asked to participate in the collection of blood specimens; however only those centers equipped to handle the specimens will participate in this aspect of the study.

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Blood specimens will be acquired at three time points during the study: 1)pre-op (this specimen can be acquired at any time prior to the induction of anesthesia, e.g. at the pre-op testing session, or in the OR when the IV is inserted). 2)Postoperative day 1 and 3)Postoperative day 2. The postoperative samples should be acquired along with the standard morning blood draw if ordered to minimize the inconvenience and risk of blood drawing. We will be acquiring two types of samples at each time point for this study. No specific analyses are planned at this time. Blood specimens are not required by the study, although all centers should attempt to collect complete sets of specimens.

A total of 17 cc of blood are collected at each visit. 8.5 cc specimens will be placed in each of two PaxGene tubes.

A. Required Blood Collection Accessories

1. Blood collection set such as the BD Vacutainer® Safety-Lok™ Blood Collection Set.
2. A BD Vacutainer® Needle Holder or equivalent must be used to ensure proper function.
3. Labels for positive donor identification of samples (an email template is provided, labels will be sent with plasma/serum storage tubes)
4. Alcohol swab for cleansing site
5. Dry sterile gauze
6. Tourniquet
7. Needle disposal container for used needle or needle/holder combination

B. Procedure for Specimen Collection

Two tubes of blood are collected at each time point. The two specimens are:

DNA specimen – Pax gene blue topped tube
RNA specimen – Pax gene red topped tube

The RNA specimen should always be collected last.

Follow standard phlebotomy procedures for your institution. If possible, incorporate the acquisition of these specimens with clinical phlebotomy in order to minimize pain and inconvenience to the participant.

Labels are provided. Use a permanent marker to add the date collected and the patient number to the labels.

DNA tubes: PAXGene Blue topped tube

After blood collection, gently invert the PAXgene Blood DNA Tube 8 - 10 times.

Make sure the tube is labeled appropriately.

Store upright at room temperature (18-25°C) until the RNA tube and other tubes are ready to freeze.

RNA Tube PAXgene Red topped tube

Immediately after blood collection, gently invert the PAXgene Blood RNA Tube 8 – 10 times.

Store the PAXgene™ Blood RNA Tube upright at room temperature (18°C to 25°C) for a minimum of 2 hours and a maximum of 72 hours before processing.

Make sure the tube is labeled appropriately.

D. Freezing specimens

All two labeled specimens (DNA and RNA) should be stored on their side (not upright in a rack) in a regular (-20°C) freezer.

After 24 hours specimens can be transferred to a deep freezer (-70°C)

E. Shipping Specimens

Specimens will be shipped to Mount Sinai on a regular basis.

Each center should have one individual who is certified to ship biological specimens (i.e. IATA/DOT).

Shipping kits will be sent to the centers. The basic kit that we have purchased includes a cryogenic box, The shipping kit is IATA and DOT compliant.

At a convenient time on either a Monday or Tuesday, each center should transfer their specimens to the Styrofoam container, fill the remainder with crushed dry ice, close the container properly and ship to Mount Sinai. Shipments, even those sent overnight, after Tuesday runs the risk of arriving during the weekend so please ship on Monday or Tuesday.

* To calculate the number of rpm necessary to attain 1000 g, use the following formula: $\text{rpm} = 9450/\sqrt{r}$, where r is the distance in centimeters from the center of rotation to the bottom of a test tube when it is extended in the centrifuge head.

Example: if r = 16, then rpm = approximately 2400.

Mailing instructions will be provided.

4.3.6. Neurocognitive Assessment

4.3.6.1. Data Collection Schedule

Data	Pre-op	Pre-op DoS	OR	PACU	POD1	POD2	POD 3-5 If (possible)	3 & 6 months
Demographics	X							
History Physical & Lab Data	X							
MCI Determination	X							X
GDS short form	X							X
Charlson Comorbidity	X							
Delirium Battery	X			X	X	X	X	X
Socioeconomic Status Cognitive Battery	X							X
Drug Dosages	X							X
Time fit to leave PACU				X				
QoR Score				X				
VAS	X			X	X	X	X	X
Morbidity and Mortality								X

4.3.6.2. Cognitive Testing Battery

Selection of Cognitive Outcomes Measures: Based on our previous international study, we have chosen cognitive measures from the domains that were found to be maximally sensitive to POCD. The domains that were most sensitive include: verbal learning and working memory, episodic memory, processing speed, and set shifting. These same domains are assessed in the neuropsychological battery of the Unified Data Set (UDS) for which we currently have data on over 1300 US adults with normal cognition, over 600 with MCI and an additional 200 with other cognitive impairment. This rich data set will provide a robust normative sample against which to compare our sample. It will provide a basis for standardization including adjustment for demographic variables (age, education and gender) and robust estimates of the variance for the measures. In addition, the battery will be administered repeatedly to this large cohort and estimates of performance for repeated measures will be available to supplement our experience for change estimates. Composite Z scores will be created for data reduction and these measures can be compared to the existing larger sample to insure that we have a representative estimate of performance at baseline. In addition it will allow us to determine an effect size for POCD in the untreated population and examine the impact of POCD as a measure of change.

Two versions of the battery are available for use, one designed for in-person interview and one designed for use over the telephone, If possible, the in-person battery is preferable for all participants. For participants who would not be able to participate due to inability to participate in in-person interviews at the 3 and 6 month visit, the telephone battery may be substituted. If the team knows that the patient

will not be able to do the 3 and 6 month visit, the preoperative testing session should be accomplished using the telephone battery. The telephone battery requires additional training and certification to use, as noted below.

The batteries are described below:

A) In-Person Battery

1. **Logical Memory Test** (Immediate and Delayed Paragraph Recall). The Logical Memory is a modification of the episodic memory measure from the Wechsler Memory Scale-Revised (WMS-R). Free recall of one short story (Story A) that consists of 25 bits of information will be elicited immediately after it is read aloud to the participant and again after a 15-20-minute delay. The total bits of information from the story that are recalled immediately and after the delay interval are recorded (maximum score of 25 each).
2. **The CERAD Word List Memory Test** is a free recall memory test that assesses learning ability for new verbal information (Welsh et al., 1994). A ten-item word list is presented over three trials (at the rate of 1 every 2 seconds) with a different word order each trial. The participant is instructed to read each word aloud as it is presented and then asked to recall as many words as possible. The maximum number of correct responses is 10 for each trial, with a Trial Total of 30. Word List Delayed Recall: the participant is asked to recall as many of the 10 words as they can. Word List Recognition: Immediately after the Delayed Recall task, the participant is asked to identify the 10 words from the list of target words and ten distractor words. There is a maximum of 10 correct 'Yes' responses and 10 correct 'No' responses. To adjust for chance, the participant's score is calculated as the total number of correct answers minus 10. A Savings score is calculated to reflect the ability to recall learned information after a delay; this score is obtained by dividing the number of words recalled after the delay by the total number correct on Trial 3.
3. **Boston Naming Test.**¹²⁸ This measure of visual confrontation naming requires the participant to name objects depicted in outline drawings. In our modification of the full BNT, only 30 items are presented (only the odd -numbered items from the full 60-item test). The drawings are graded in difficulty, with the easiest drawings presented first. The number of spontaneous correct responses (maximum score = 30) and spontaneous plus semantically-cued correct responses (maximum score = 30) are recorded.
4. **Category Fluency Test** This is a measure of verbal fluency in which the participant is asked to generate exemplars from each of two semantic categories (animals and vegetables) in successive one-minute trials. The primary performance measure is the number of correct, unique exemplars generated for the two categories.
5. **Digit Span Test** The Digit Span subtest from the WAIS-R requires the participant to repeat sequences of single-digit numbers which are read aloud by the examiner. In the Forward condition, the participant must repeat the digits in the same order; in the Backward condition, the digits must be repeated in the reverse order. **The sequence length** increases from three to nine digits in the Forward condition, and from two to eight digits in the Backward condition, with two trials presented for each sequence length. A point is awarded for each sequence correctly produced, so the maximum score for each condition is 14 points.
6. **Trail Making Test: Parts A and B.**¹²⁹ Part A consists of 25 circles numbered 1 through 25 distributed over a white sheet of 8 1/2" X 11" paper. The participant is instructed to connect

the circles with a drawn line as quickly as possible in ascending numerical order. Part B also consists of 25 circles, but these circles are either numbered (1 through 13) or contain letters (A through L). Now the participant must connect the circles while alternating between numbers and letters in an ascending order (e.g., A to 1; 1 to B; B to 2; 2 to C). Time (in seconds) required to complete each trail and by the number of errors of commission and omission is recorded. Maximum time for Part A is 150 seconds and for B is 300 seconds.

7. **Digit Symbol Substitution Test** This subtest from the WAIS-R consists of 110 small blank squares (presented in seven rows) each randomly paired with one of nine numbers (1 to 9) printed directly above it. Standard administration will be used and the score is the number of blank squares filled in correctly within 90 seconds (Maximum raw score = 110). This test engages multiple cognitive abilities including attention, psychomotor speed, complex scanning, visual tracking, and immediate memory.

B) Telephone Battery:

Note: Coordinators must be additionally credentialed by the Cognitive Battery oversight group (M. Sano, PhD, M Sewell, PhD, and S Deiner MD) prior to engaging in cognitive testing over the telephone.

1. **Logical Memory Test** (Immediate and Delayed Paragraph Recall). The Logical Memory is a modification of the episodic memory measure from the Wechsler Memory Scale-Revised (WMS-R). Free recall of one short story (Story A) that consists of 25 bits of information will be elicited immediately after it is read aloud to the participant and again after a 15-20-minute delay. The total bits of information from the story that are recalled immediately and after the delay interval are recorded (maximum score of 25 each).
2. **The CERAD Word List Memory Test** is a free recall memory test that assesses learning ability for new verbal information (Welsh et al., 1994). A ten-item word list is presented over three trials (at the rate of 1 every 2 seconds) with a different word order each trial. The participant is instructed to read each word aloud as it is presented and then asked to recall as many words as possible. The maximum number of correct responses is 10 for each trial, with a Trial Total of 30. Word List Delayed Recall: the participant is asked to recall as many of the 10 words as they can. Word List Recognition: Immediately after the Delayed Recall task, the participant is asked to identify the 10 words from the list of target words and ten distractor words. There is a maximum of 10 correct 'Yes' responses and 10 correct 'No' responses. To adjust for chance, the participant's score is calculated as the total number of correct answers minus 10. A Savings score is calculated to reflect the ability to recall learned information after a delay; this score is obtained by dividing the number of words recalled after the delay by the total number correct on Trial 3.
3. **Category Fluency Test** This is a measure of verbal fluency in which the participant is asked to generate exemplars from each of two semantic categories (animals and vegetables) in successive one-minute trials. The primary performance measure is the number of correct, unique exemplars generated for the two categories.
4. **Digit Span Test** The Digit Span subtest from the WAIS-R requires the participant to repeat sequences of single-digit numbers which are read aloud by the examiner. In the Forward condition, the participant must repeat the digits in the same order; in the Backward condition, the digits must be repeated in the reverse order. The sequence length increases from three to

nine digits in the Forward condition, and from two to eight digits in the Backward condition, with two trials presented for each sequence length. A point is awarded for each sequence correctly produced, so the maximum score for each condition is 14 points.

5. **Oral version of the Trail Making Test: Parts A and B.**

In the Oral version of the trails, the participant is asked to count from 1-25 as fast as possible. Timing as soon as the operator says "Begin." If a mistake is made, stop the participant and have him or her continue with the series from the last correct number. The timing is continued during corrections. Record the total time required to complete the series, including the time to offer corrections. Discontinue if task is not completed in 4 minutes.

In the second part, the participant is asked to switch between numbers and letters as in : 1, A, 2, B, 3, C, and so on until they reach the number 13. Start timing as soon as you say "Begin." Correct mistakes by saying "Go back to (last correct item) and continue from there". If participant breaks set (i.e., stops alternating) then say, "Go back to (last correct item) and continue from there. Remember, you are switching between numbers and letters." Record time to completion as with TMT-A. Discontinue if task is not completed in 4 minutes.

In addition, there is a telephone version of the MMSE called TICS which will be employed when using the telephone battery. All other tests used during the preop and 3 and 6 month follow-up tests can be done over the phone using the original instruments (e.g. GDS, SF-36)

Training of Staff for Psychometric Testing. We will use the standardized techniques for the training of staff in testing methods. This includes the use of available training tapes, a well developed manual for testing procedures and a plane for certification to insure all assessors are adequately and comparably trained. Continuing supervision will be provided by Mary Sano, who is experienced in delivering comparable supervision for national and international multi-centered clinical trials. In addition, language clarity is crucial to effectively using the telephone screening battery. Therefore, all coordinators need to be evaluated by the cognitive battery oversight group (M. Sano, PhD, M Sewell, PhD, and S Deiner MD) prior to engaging in cognitive testing over the telephone. This group will assess the clarity and capacity of the language skills necessary to effectively use the telephone battery.

Timing of the post intervention cognitive assessment. As the reviewers mentioned, acute effects of the treatment may include drowsiness, which could interfere with the cognitive assessment. We have chosen to conduct the initial cognitive assessment at 3 months (+/- six weeks) post surgery because this interval is sufficiently long to avoid drug effects as well as effects of any acute post surgery events. This interval is conventionally used to avoid acute effects of cardiovascular and cerebrovascular events on cognition. The second assessment at 6 months(+/- ten weeks) will permit the assessment of the persistence of treatment effect and of deficit should it exist.

Diagnosis of MCI and other Cognitive deficit categories: At baseline, 3 and 6 months a diagnosis of MCI will be made. This will include a self and informant reported evaluation consisting of a questionnaire which will include an assessment of memory complaint. Specifically, the participant will be asked 1) if they have memory problems, 2) if this is a change and 3) whether they believe their memory to be worse than age-matched peers.

All subjects will receive the **Mini-Mental State Exam (MMSE)**.¹²⁴ The MMSE is a fully structured screening instrument frequently used for Alzheimer's disease drug studies. The MMSE is scored as the number of correctly completed items, with lower scores indicative of poorer performance and greater cognitive impairment. The total score ranges from 0 to 30 (perfect performance). This along with performance on the Logical memory test will be used to categorize amnesic MCI. Cut-offs will

be based on age and education and will be taken from the current ADNI study and the ADCCS MCI study, both of which have proven successful in identifying MCI populations with rapid transition to AD. In addition, subjects who fall below expected ranges on the MMSE will be worked up by local experts who are familiar with the UDS, and will make an independent diagnosis of cognitive function consistent with ADC criteria. Specific categories include: MCI amnestic, non-amnestic, single and multiple domains. These categories will be adjudicated by the ADRC consensus conference team at MSSM. This team has a 25 year history of diagnostic expertise. It has trained clinicians and psychometrists in test administration and the application of diagnostic criteria. It is expected that no more than 10 % will require this evaluation and review. It should be noted that only subjects with frank dementia will be excluded. All others will be included and classified as described above. Specific analyses and aims are based on the amnestic MCI only because it is the best characterized. However the effect of prevalent and incident categorical cognitive criteria will be examined in exploratory analyses.

4.3.6.3. Preoperative Visit

Eligibility and the documentation of consent will be confirmed at the preoperative visit. During this visit, patients will provide demographic and historical medical information, including information regarding medication usage. The cognitive and delirium testing batteries as well as the classification instruments (GDS, Charlson) will be performed. During the preoperative period we also do the verbal analog scale (VAS), MCI Determination, and SF-36. The testing should occur in a quiet room and will take approximately 90 minutes for the first visit. The pre operative blood samples can be obtained up to immediately before surgery. For patients who require the cognitive testing to be done over the telephone, a separate consent document with an alteration of documentation (i.e. waiver of signature) is available for only for the preroperative testing section. The participants must be clear that there is a larger study in progress and that they will have to sign consent documents before any other procedure can be done.

4.3.6.4. Post Anesthesia Care Unit (PACU)

In the PACU patients will be assessed using instruments specific for the PACU, (Fitness for Discharge, Quality of Recovery Score, Verbal Analog Scale for pain) and an abbreviated Delirium Battery consisting of the CAM-ICU and MMSE (leaving out the drawing). The testing time will be from 45 minutes to 90 minutes after arrival in the PACU, depending on the patient's recovery and will last about 8 minutes.

4.3.6.5. In-hospital Postoperative Evaluation

Patients will be visited each day. The verbal analogue scale for pain will be employed and the full Delirium Battery will be employed. The Delirium Symptom Interview (DSI) and the MMSE will be used. The first 18 questions of the DSI are asked directly of the patient. The remaining questions are observations on the part of the examiner. Once the coordinator leaves the patient testing session, then the Memorial Delirium Assessment Scale and the CAM should be completed. Blood specimens should be collected on postoperative day 1 and 2. Delirium assessments will continue for the patient

as long as they are in the hospital to the extent possible up to POD 5. Once a patient is determined to have delirium, further assessments are not necessary. POD 1 and 2 are the most important, but if possible continue the assessment for additional days up to and including day 5.

4.3.6.6. 3 and 6 Month Visits

During the follow-up visits information regarding the patients' current medication usage will be obtained, along with any complications that may have occurred since the patients' surgical date. The cognitive and delirium testing batteries, as well as, the classification instruments (GDS, SF-36, VAS) will be administered. This testing session takes approximately 60 minutes and should be conducted in a quiet room. The 3 month visit can be conducted at 3 months post operation +/- 6 weeks. The 6 month visit can be conducted at 6 months post operation +/-10 weeks. If the participant is not available for an in-person interview the telephone battery may be employed if the coordinator has been reviewed and approved by the cognitive battery oversight group.

4.4. Patient Safety Monitoring

4.4.1. Monitoring and Reporting of Anticipated Events

The common reactions to dexmedetomidine included in the consent document are:

- low blood pressure,
- high blood pressure,
- nausea and vomiting,
- slow heart rate,
- fever,
- hypoxia (not getting enough oxygen),
- fast heart rate,
- anemia (low blood level),
- dry mouth,
- producing too little urine
- thirst.

The serious reactions reported for dexmedetomidine included in the consent document are:

- very low blood pressure
- very low heart rate
- changes in the rhythm of their heart,
- difficulty breathing from fluid collecting in the lungs or around the lungs
- asthma like reaction,
- changes in the amount of potassium in their blood,
- increases in the number of white blood cells
- decreased function of their adrenal gland

Most of these events are extremely common during all forms of anesthetic care. Due to the short half-life of the drug in use, the principal area for monitoring of these events will be the OR and PACU. In order to track the safety of the intervention, the following correlations will be used.

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Low and high blood pressure – specifically requiring treatment by the anesthesiologist or PACU staff
 Very low and very high blood pressure – requiring continuous infusion therapy
 Nausea and Vomiting – 1-5 visual analog nausea scale, vomiting as observed
 Fever $\geq 38^{\circ}\text{C}$
 Hypoxia – 90% or less for > 5 min
 Anemia $< 8\text{g/dL}$ hemoglobin
 Arrhythmia – as observed
 Potassium levels outside of normal range
 White cell count outside of normal range
 Urine output < 50 ml/hr

Dry mouth and thirst are so common, admittedly annoying, but to date not associated with any organ specific or other physiologic outcome. They will not be specifically tracked as part of the safety analysis. Decrease in adrenal function is rare and there is no simple test to follow adrenal function. The study physicians will be aware of the possibility should signs of adrenal dysfunction occur.

The following schedule will be used to note anticipated adverse events

	OR	PACU	Hospital Stay
Low and high blood pressure	X	X	
Very low and very high blood pressure	X	X	
Nausea and Vomiting	X	X	X
Fever $\geq 38^{\circ}\text{C}$		X	X
Hypoxia – 90% or less for > 5 min	X	X	
Anemia $< 8\text{g/dL}$ hemoglobin	X	X	X
Arrhythmia – as observed	X	X	
Potassium levels outside of normal range		X	X
White cell count outside of normal range		X	X
Urine output	X	X	

These items will be included on the case report forms, which should be completed in a timely manner and transmitted to the DCC. The expected adverse events will be summarized and presented to the DSMB on a regular basis. In the absence of a finding of an unanticipated problem, the DSMB assessments will be distributed to the sites for submission to individual IRBs within 1 month of the DSMB meeting. Blinded complications of the ongoing adverse event experience will be available to sites should they need additional information for the human subjects protections review. Each site investigator should assure that this study complies with their institutional reporting requirements regarding adverse event reporting.

4.4.2. Record and Reporting of Serious Adverse Events

A serious adverse event is any event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Any serious adverse event occurring from the beginning of the study, until hospital discharge should be recorded on the serious adverse event form. This form should be faxed to the CCC and DCC within 24 hours of the investigator or other member of the study team becoming aware of the event. Each site investigator should assure that this study complies with their institutional reporting requirements regarding adverse event reporting. Unless otherwise required by the institution, notification of Hospira, Inc and federal authorities will be handled by the CCC. Documentation of these communications will be provided to the centers on request.

4.4.3. Reporting of Unanticipated Problems

This study is funded by the National Institutes of Health and therefore subject to the human subjects regulations found in 45 CFR 46.103(b)(5) that require regulations prompt reporting to the IRB, the institutional official, and the Office for Human Research Protections of *any unanticipated problems involving risks to subjects or others*. The Office for Human Research Protections (OHRP) considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Those problems that are unanticipated based on severity and/or frequency of otherwise expected events will be captured by the plan for monitoring expected events. The investigational staff should clearly understand that unanticipated problems may be distinct from adverse events, primarily in that the event may suggest greater risk without having caused medical harm. For examples of unanticipated problems that do not involve adverse events but must be reported under the HHS regulations see [Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#).

Any unanticipated problem should be reported to the CCC within 24 hours of the investigational staff becoming aware of the problem. The CCC will direct the sites as to additional other documentation that may be required. The principal investigator will notify the chairman of the DSMB. Each site investigator should assure that this study complies with their institutional reporting requirements regarding reporting of an unanticipated problem. Unless otherwise required by the institution, notification of Hospira, Inc and federal authorities will be handled by the CCC. Documentation of these communications will be provided to the centers on request.

5. Data Management and Statistical Analysis

5.1. Manual of Procedures

The CCC and Study Chair with input from the clinical personnel will identify procedures that are not represented in the existing Manual of Procedures (MOP) and discuss how to design the new procedures.

5.1.1. Revising and reviewing procedures

The CCC will revise the MOP based upon changes to the FDA regulations, International Committee on Harmonization (ICH) Good Clinical Practices (GCP), and NIH Guidelines, as well as changes to the protocol. The revised MOP procedures will be presented to the clinical personnel at each site for discussion. The revised MOP will be submitted to the local IRB for approval. Each site is responsible for submitting the initial protocol and each amendment to their IRB for approval.

5.1.2. Training and implementing procedures

All research personnel are required to review (read and understand) the MOP for this study at each investigational site. This will be documented by a Training Compliance Form that the personnel will complete after their review of the MOP. All their questions concerning the MOP will be answered by the Study Chair or the DCC.

5.1.3. Distribution

All copies of the MOP will be on the study website (<http://www.dexlirium.org/>). The study website will be the method in which study information, including protocol updates are distributed to the study centers.

Each set of updates will be delineated in a document and placed on the study website,.

The lead center will send out an e-mail to all centers informing them of updates to the study website.

5.1.4. Documentation

The most recent version of the MOP will be located on the study website (<http://www.dexlirium.org/>). The website will be maintained by the lead center, Mount Sinai School of Medicine. The website will house all previous versions of the MOP.

A master copy of the MOP will be maintained, on the study website, at the DCC and at Mount Sinai along with records of all previous versions. The footer of each page will contain the version date and the page number. The DCC is responsible for maintaining a record of MOP training and review for all research personnel at each investigational site.

The Data Coordinating Center for this study will be the Department of **OUTCOMES RESEARCH** at the Cleveland Clinic. It will be responsible for the following activities:

- ❖ Case Report Form (CRF) development
- ❖ Database development
- ❖ Data handling
- ❖ Training site personnel on CRF completion

5.2. Statistical Analysis Plan

5.2.1. Description of Study Population

All data on patients enrolled in this study will be summarized separately for those randomized to treatment with dexmedetomidine and those randomized to placebo, and also stratified by Hospital/Center. Categorical variables will be described in terms of percentages, and quantitative variables in terms of median and range or mean and standard deviation, as appropriate. Consistency among sites will be checked on all outcome measures and relevant factors and covariates. If substantial site effects are evident, data analyses will be stratified by site, or indicator variables for sites will be included in the models. All statistical procedures will be implemented using SAS software for the PC.

5.2.2. Data Analysis

5.2.2.1. Specific Aim I

The primary goal of the statistical analyses for this Specific Aim is to test whether treatment with dexmedetomidine influences the chance of developing PD in this population. Before proceeding with the statistical analyses, the proportions of patients who developed PD will be described with regard to personal and clinical characteristics (age, gender, type of surgery, pre-entry medications, ASA, etc.) These descriptive analyses will provide insight into the data and help identify important covariates.

A logistic regression model will be assumed, with outcome defined as the presence or absence of PD, and treatment with dexmedetomidine as the primary factor of interest. Since this is a randomized trial, covariate history in the treatment and control groups should be balanced, but the data will be explored to see if some covariates have sufficient influence to warrant inclusion in the model. The influence of covariates on the effectiveness of treatment with dexmedetomidine will be tested by adding terms for the covariates and covariate*treatment interaction terms to the model.

5.2.2.2. Specific Aim II

(1) Primary Analysis. The primary goal of the statistical analyses for this Specific Aim is to test whether treatment with dexmedetomidine influences the rate of change of cognitive function in this population. Cognitive function is quantified by a normalized composite score defined from the neuropsychological test battery. The test battery consists of 7 tests: Logical Memory Test, CERAD Word list Memory Test, Boston Naming Test, Category Fluency Test, Digit Span Test, Trail Making Test and Digit Symbol Substitution Test. Patients will be given these tests at each of the 3 pre-specified assessment time points (before surgery, 3 months and 6 months after surgery). The calculation of the composite score of the cognitive function has two normalization steps: 1) Normalization of each of the 6 individual test scores. For each patient at each time point, we use the individual test score, subtract the mean score from The Uniform Data Set (UDS), and divide the results by the SD from the same dataset to obtain a normalized score for each test, and then we sum them up over different tests to get a total of the normalized scores. 2) Normalization of the total of the normalized scores. The step proceeds by subtracting the mean of the baseline total score and dividing the results by the SD of the baseline total score. We call this resulting score the composite Z score. Notice that the composite Z score has zero mean and unit variance at baseline.

The primary analytic technique for the analysis of the change of the composite Z scores over time will be Generalized Estimating Equation (GEE). This statistical method permits the analysis of data from multiple visits per patient and takes into account the fact that measures of the dependent variable (i.e. the composite Z scores) of a single individual over time are likely to be correlated with one another. The repeated measures for each subject are treated as a cluster. A second advantage is that even if the correlation is mis-specified, the GEE will still provide consistent estimators of the regression parameters. Third, the GEE can handle missing data (missed visits) very easily.

The primary analysis will be an intent-to-treat (ITT) analysis. Individual subjects will be analyzed in the group they are randomized to regardless of drop-in or dropout status. A list of covariates anticipated to be associated with rate of change in the composite Z score in this study has been compiled. These variables will be included as covariates in the GEE analysis if found to be moderately associated with response ($P < .15$). All baseline variables will also be assessed as potential confounders. Those found to be associated with treatment group ($P < .1$) and with response ($P < .15$) will be included too.

(2) Secondary Analysis. In addition to the primary ITT analysis, as a confirmatory analysis and to allow comparison with other rates of change in this study, both a completers and compilers analysis will be conducted as a secondary analysis. Secondary subgroup analyses will examine the influence of sex and education on the cognitive change.

Besides the primary analysis the composite Z score as described above, in the secondary analysis, we may investigate other important composites such as: memory composite is a combination of verbal learning and delayed recall, and attention/executive function is a composite of the other 4 scores. Also, we may examine different weighting schemes to combine the elements as a new composite.

To assess the impact of PD on the POCD, we may include the PD status as a covariate in the GEE model in the secondary analysis. The dependent variable can be any of the important composite scores.

5.2.2.3. Secondary Aim

To study the role of preexisting cognitive impairment on the chance of developing PD or POCD, measures of cognitive impairment and their interaction with treatment will be added to the covariates identified as significant in the models constructed for Specific Aims I and II. For this purpose, cognitive impairment will be characterized once as a quantitative variable equal to the overall composite score at baseline, and once as a binary variable, with cutoff determined by the diagnostic categories from the UDS-like evaluation, which includes amnesic MCI, non-amnesic, single domain and multi domain, the traditional definition of MCI. The data will also be explored for evidence that the presence or absence of PD in conjunction with MCI influences the subsequent POCD findings.

5.2.3. Sample size and statistical power

We anticipate a sample size of approximately 706 patients, half randomized to treatment with dexmedetomidine and half randomized to placebo. A .05 significance level will be applied to statistical tests of the main effects from the linear and logistic regression models in Specific Aims I and II. All tests will be 2-tailed.

5.2.3.1. Specific Aim I

Test of difference in PD incidence between treated and placebo groups. Previous data suggest that the incidence of PD in elderly surgical patients is around 15%. If that is the rate in our placebo group, samples of size 353 in each of our 2 groups will have 80% power to detect a significant treatment effect if treatment reduces the PD incidence rate to 8% or less. Given the experience of the original delirium prevention trial in which a 400% decrease was noted,¹⁷ a less than 50% decrease is reasonable and not significantly higher than a previously published trial of non pharmacologic intervention.¹³⁰

5.2.3.2. Specific Aim II: Effect size and sample size.

To use the GEE model to assess the repeatedly measured composite Z scores, we need to assume the correlation structure of the repeated measurements over time. From the ISPOCD studies, we can estimate the correlation between the preoperative score and the 3-month follow-up score is 0.556. Although the components of POCD test battery differ from what we are proposing here, it is reasonable to assume this moderate correlation in our study. In fact, to be conservative, we choose to use correlation 0.6. And the correlation structure is assumed to be AR(1), meaning the correlations between the first and the second and between the second and the third measurements are equal to 0.6, while the correlation between the first and third measurements is 0.36(=0.6*0.6). Since the baseline cognitive test is given before the treatment and placebo is assigned, the main effect of the treatment can be assumed to be zero. Also from the ISPOCD dataset, the mean of the standard deviations of the composite scores was estimated as 2.50 and the slope for the placebo group was - 0.50. We are assuming the standard deviation of the composite score does not change over time. So

Change Rate of the composite Z score	0.1	0.12	0.14	0.15	0.17	0.18	0.19
Power	0.47	0.62	0.75	0.81	0.9	0.92	0.95

the relative change in the placebo group was set to $-0.20(=-0.50/2.50)$. Based on these data, we provide in the following table a sensitivity analysis for the effect size given $\alpha=0.05$ (two tailed) and the sample size ($N=353$ for each group) specified in the Specific Aim I. Power calculation was based on the formula on Page 30 of Diggle, Liang and Zeger.¹³¹ The dropout rate is estimated at 30% between each follow-up.

Based on the proposed sample size ($N=353$) in Specific Aim I, we will be able to have 81% power to detect a rate of change 0.15 in the composite Z score.

5.2.3.3. Relative Change in the composite score in terms of the original test score scale

In fact, the power calculation presented above is valid for the analysis of any individual or composite score as long as it is normalized in the same way as we derive the composite Z score. We do not have the pilot data to see the rate of change in the scale of the original composite Z score, but for the individual component of the neuropsychological test battery, we list the change in the real scale in the following table-the rate is set to 0.15. The means and SDs of different tests come from the UDS study.

Test	Mean	SD	Change in rate=0.15
Digit Span Forward - # Trial Correct	8.6	2.1	0.3
Digit Span Backward - # Trial Correct	7	2.2	0.33
Category Fluency-Animals	20.2	5.8	0.87
Trial Making Test-Part A	34.5	15	2.25
Trial Making Test-Part B	87.2	44.8	6.72
WAIS-R-Digit Symbol	46.5	12.4	1.86

5.2.3.4. Missing data assumption

The GEE model assumes that the probable value of any missing outcome does not depend on any previous (or succeeding) outcomes: missing completely at random (MCAR).¹³² If data are missing at random (MAR) (when the probable value of the missing outcome depends on observed outcomes, such as observed outcome at baseline and/or previous visits), or if data are missing in non-ignorable fashion, i.e. the probability of missing depends on the unobserved outcomes, straight GEE inference based on the observed data is not valid.^{133;134} The analysis will include an assessment of MCAR by fitting logistic models with missing data indicators as dependent variable.¹³⁵ If deemed necessary, it is possible to calculate consistent treatment estimates in GEE under MAR using the multiple imputation method.¹³³

Secondary Aim: Statistical power estimates for testing the influence of MCI on the occurrence of PD in our sample of around 700 patients are based on assuming a 10% incidence of MCI in this population and a 15% incidence of PD among patients randomized to placebo. That combination constrains the possible differences between the proportion of patients with MCI who develop PD and the corresponding proportion among the MCI negative patients. (For example, if the incidence of PD among 35 MCI-positive placebo patients is 30%, the corresponding incidence among 315 MCI-negative placebo patients must be 13.3% for the overall incidence to be 15%.) Statistical power was

estimated separately under two assumptions about the effect of dexmedetomidine: (1) no effect, so treated and placebo patients both have a 15% incidence of PD, and (2) treatment reduces the PD incidence by half (as in the sample size calculations for Specific Aim I.). In either case, our sample sizes provide at least 85% power to detect a 2.5-fold difference in incidence of PD. That is, for example, 30% of MCI-positive patients vs. 13% of MCI-negative patients if dexmedetomidine does not influence the incidence of PD, and 25% vs. 10% if it does.

6. Study Management

6.1. Database Development

Outcomes Research personnel will program a custom-designed relational database for data entering and auditing. The database will be housed on a secure server that is backed-up to tape weekly. The database will be password protected at several administrative levels. The passwords will be designed such that a blinded individual can view appropriate data and not break the blind. Only the Research Manager, Research Coordinator, and Director will be able to change the database format once it is in use. All changes will be made as a collaborative effort with the Study Chair and investigators.

The database will be designed using the protocol and CRF as guidelines for the information format. The database will be programmed to screen data for appropriate values as they are entered. List views will be available to configure the data for presentation of critical information.

6.2. Data Handling Process

At the beginning of the trial the steering committee will be directing how the study should be started and conducted. As data is collected, it will be submitted to the Data Coordinating Center (DCC) from each site. The DCC will process the data and clarify any discrepancies with the sites. Reports will then be submitted to the DSMB. The DSMB will make any recommendations to the Steering Committee on how conduct of the trial should change. The Steering Committee will have the responsibility of sharing this information with each individual site.

6.3. Submission of Data to the DCC

The original written Case Report Form (CRF) pages will be maintained at the sites. Data will be entered into the database within one week after completion of the original CRFs. Each center will enter their data via a secure website. If there are any discrepancies or missing data the DCC will query the sites to obtain appropriate explanation or missing information (see Transmitting CRFs to the DCC, Section 6.3.2).

All study data should be entered directly onto the Case Report Form (CRF) for this study. Each patient visit will have pages of the CRF associated with the data to be recorded. All data should be recorded with no fields skipped or left blank. If the investigator wants to submit additional data to the DCC that is not requested on the CRF, the investigator/ site may do so by submitting a memo detailing the additional changes.

If data required on the CRF pages are unavailable, every effort should be made to obtain the necessary data. If the data are permanently missing, indicate so by placing the word "unknown" or as otherwise directed on the CRF page for that field.

All changes to CRF pages must be stricken through, initialed, and dated per Good Clinical Practice (GCP) guidelines. Strike through the entire data field when making corrections. No use of white out is permitted. Only site personnel can make changes to the site-completed CRF pages. All CRF pages should be completed using black ink. Pencil is not acceptable.

Data entered into the database will be electronically submitted to the DCC on a monthly basis before the 15th of each month by each site.

Site personnel will copy the original CRF. A copy will then be sent with a complete CRF transmittal form to the DCC for processing.

6.3.1. Case Report Form (CRF) Completion Guidelines

All data recorded on the Case Report Form (CRF) will be collected at the clinical sites. All forms completed at the clinical sites should be checked by the site's CRC before entry into the study database.

6.3.2. Transmitting CRFs to the DCC

Once the CRF pages are entered and submitted to the DCC, no changes can be made on them. This will be verified by checking the date on the database entry. If there are any data changes to be made, the site can send the DCC a corrected CRF accompanied by a memo detailing the changes. Should the DCC require additional changes to the same CRF they should submit another set of queries.

A set of queries will be faxed or emailed to the site for clarification by the DCC. After the clarification is made, the site will maintain the signed and dated original and send a copy to the DCC for entry. Every effort should be made by the site to reply to the queries within 1 week of receipt. The query and all associated correspondences will become part of the CRF for that patient. The query should be filed with the corresponding patient visit to become part of the source documentation.

The DCC should generate a query if any of the following situations occur:

1. The database "flags" an unexpected value in the data.
2. The data entry personnel "flag" unexpected or unreadable values on the submitted CRF page from the site.
3. The data entry personnel discover an empty field or missing CRF page.

The site should submit a corrected CRF if any of the following situations occur:

1. Additional information and/ or corrections are needed to the data submitted on the original CRF.
2. Previously unreported, incorrectly transcribed, or missing data are discovered at the site.
3. The site is providing additional information to the DCC to clarify an Adverse Event or Serious Adverse Event.
4. A protocol deviation is identified. (This should also be entered on the Protocol Deviation Log and reported to the local IRB and CCC)

The monitor should generate a query if any of the following situations occur:

1. Discrepancies are identified on the CRF during a monitoring visit.
2. CRFs have been completed incorrectly.
3. Adverse Events or Serious Adverse Events require further clarification from the site.
4. A protocol deviation is identified. (This should also be entered on the Protocol Deviation Log and reported to the local IRB)

6.4. Regulatory Oversight and Auditing

All data will be audited to confirm consistency among patient records, the study's Case Report Form (CRF) pages, and the main database maintained at the DCC.

Central monitoring will consist of evaluating case-report forms for completeness and range-checking results. At interim analysis points, statistical procedures will be used to compare results from individual sites

6.4.1. Central Monitoring

The CCC and DCC will conduct audits on the regulatory file and data files for this study for all sites respectively. The investigators will submit all documentation related to the enrollment and conduct of the study to the DCC. The Research Manager, Coordinator, or designated support staff will review the datasheets and regulatory logs for each study patient for any missing data, discrepancies or improper documentation.

The designated support staff will enter the patient information in a custom database.

If there is any missing datum, a query will be made to the investigator listed on the datasheet to obtain the missing item. The investigator should write a response to the query, sign it, and mail it to the Research Coordinator at the DCC. The investigator should keep a copy at the site as part of the patient's CRF.

Hard copy forms will be stored in file cabinets within a secured area at the Department of **OUTCOMES RESEARCH**. To protect automated records and files against loss, Outcomes Research will generate weekly backup onto tape. In the case of a disk failure, only data written to the files since the last backup will be subject to loss and can be easily restored. The DCC will provide protection of all databases through electronic measures using a multi-layered, but simple approach: all study related files will reside on the database server rather than on individual hard disk drives and the files will be protected by the operating system features against general access. User names will be password protected. Access to directories will be strictly monitored according to need.

When enrollment for the project is complete, the Research Manager and Research Coordinator will conduct a final data audit to assure that all data are accurate and all queries have been resolved. The Statistician then will perform a final analysis of the data. If there are any inconsistencies, the hard copies will be accessed and reviewed by the Statistician, Investigators, CRCs, and personnel at the DCC.

6.4.2. On-Site Monitoring

Periodic monitoring will be performed. As deemed necessary, monitoring may be by phone, video conference, or on-site. During monitoring, all documentation related to consenting and trial conduct will be reviewed. The monitor, in accordance with the study requirements, will ensure that the trial is conducted and documented properly by carrying out the following activities:

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- ❖ Acting as the main line of communication between the clinical sites and the DCC
- ❖ Verifying that the clinical trial material is being handled properly
- ❖ Verifying that the investigators are following the approved protocol and any amendments
- ❖ Verifying that written informed consent was obtained before each patient's participation
- ❖ Insuring that all study documentation has been distributed to the clinical sites
- ❖ Insuring that the investigator and study staff are adequately informed about the study
- ❖ Verifying that the investigator is enrolling only eligible patients
- ❖ Reporting the patient recruitment rate to the appropriate committees
- ❖ Reporting any protocol violations
- ❖ Determining whether all adverse events are appropriately reported
- ❖ Determining whether the clinical site is maintaining the proper essential documents

All of the following procedures will be followed for each monitoring visit performed at the investigational sites unless the monitor gives contrary instructions.

- ❖ The monitor will notify the site concerning the upcoming monitoring visit. A letter will be sent and faxed notifying the responsible CRC or recorder/investigator site representative of what materials should be available for the monitor.
- ❖ The site representative will be available to answer any questions posed by the monitor in relation to patient data or trial conduct. The site personnel will ensure that the site regulatory documents are up to date and available for review. The responsible Clinical Research Coordinator (CRC) or recorder/investigator will prepare all CRFs to be available for review and identify key clinical personnel likely to be involved in conducting the monitoring visit and schedule them to be available to meet the CCC's representative/monitor.
- ❖ The site representative will notify all parties related to the study that a monitoring visit would occur and identify their responsibilities for the audit.
- ❖ The site representative will provide documentation of all qualifications of the research staff involved with the study for review.
- ❖ If necessary, the site representative will give a schedule of upcoming study appointments to the monitor to facilitate firsthand knowledge of the conduct of the study.

The site representative will ensure that clinical trial material accountability records are accurate, complete and available to the monitor. The monitor will fill out the Monitoring Log at the site and obtain the designee's signature.

The monitor will submit a written report to the steering committee and the DSMB following each clinical site visit. The report will include the date, name of investigator and other individuals contacted, summary of what was reviewed, and statements concerning any significant findings, deviations, deficiencies, conclusions or actions to be taken to secure compliance.

After the monitor sends the letter containing the findings from the visit, the Principal Investigator, Sub-Investigators, responsible CRC or recorder, and other site personnel will resolve all issues. The Principal Investigator at each site will respond to the audit report as soon as possible after its receipt. They will reply to each item in the report by providing clarification or steps that will be taken to institute corrective action.

A response to any findings in the monitoring visit will be provided to the local study site, the study chair, and DSMB. All monitoring results and documentation will be kept at the site and in the Central Research File at the CCC.

6.4.3. Protocol Deviations

Protocol deviations may occur during the conduct of this study. If the site personnel are aware of any deviations, they should be reported immediately to the CCC and DCC via the Protocol Deviation Log (located in the CRF) and the local IRB using the system in place at that institution. The Protocol Deviation Log should be completed by the site personnel that identified the deviation. This log should then be signed by the Principal Investigator of that site before submission to the DCC.

Protocol deviations are made at the judgment of the site principal investigator. The site investigator has the option of getting permission from the lead center. It is however not a requirement.

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