YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Prevention Of Delirium in Inpatients Utilizing Melatonin (PODIUM) Yale HIC Protocol #1601017038			
Principal Investigator: Stephen Atlas, M.D.		**Yale Academic Appointment:** Associate Clinical Professor of Medicine	
Department: Internal Medicine, Saint Raphael Campus			
Campus Address: 1450 Chapel St. New Haven CT 06510			
Campus Phone: 203-789-3103	**Fax:** 203-789-3222	**Pager:** [redacted]	**E-mail:** stephen.atlas@ynhh.org
Protocol Correspondent Name & Address (*if different than PI*)**:**			
Campus Phone:	**Fax:**	**E-mail:**	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*)**:**			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☒ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

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See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

☐ Yes • No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

☐ Yes • No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Specify Other Yale Location:
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☒ Yale-New Haven Hospital—Saint Raphael Campus in-patient

b. External Location[s]:

☐ APT Foundation, Inc.
☐ Haskins Laboratories

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☐ Connecticut Mental Health Center ☐ John B. Pierce Laboratory, Inc.
☐ Clinical Neuroscience Research Unit (CNRU)
☐ Veterans Affairs Hospital, West Haven
☐ Other Locations, Specify:
☐ International Research Site (Specify location(s)):

c. Additional Required Documents ***(check all that apply)*****:** ☒ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC)	Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC)	Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC)	Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS	Approval Date:
☐ *Radioactive Drug Research Committee (RDRC)	Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC)	Approval Date:
☐ Yale University RSC (YU-RSC)	Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC)	Approval Date:
☐ *Nursing Research Committee	Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR)	Approval Date:

☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   13 months

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study

   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☐ Pilot ☐ Phase I ☐ Phase II ☒ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

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4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒ NCT00873379
Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)? Yes ☒ No ☐

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.*

Yes ☐ No ☒

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If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No ✱ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism

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Dr. Stephen Atlas	Yale Department of Internal Medicine St. Raphael's Campus Research Grant [redacted]	Department of Internal Medicine Grant	☐ Federal ☐ State ☒ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☒ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To: Not Applicable

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**

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NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

Stephen Atlas MD

Stephen Atlas, MD
PI Name (PRINT) and Signature

January 5, 2016
Date

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As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

Stephen Atlas MD _____ January 5, 2016

Stephen Atlas, MD _____ _____

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

ATTACHED AS A SEPARATE DOCUMENT

_____ _____

Chair Name (PRINT) and Signature Date

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Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

- **ATTACHED AS A SEPARATE DOCUMENT**

YNHH HSPA Name (PRINT) and Signature

Date

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   To investigate the efficacy of melatonin for the prevention of delirium in older adults admitted to a general Internal Medicine service.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   Introduction

   Delirium is a neuropsychiatric syndrome characterized by fluctuating disturbances in consciousness, commonly seen in hospitalized adults. It is independently associated with increased mortality, slowed recovery time, and increased hospital costs[1,2,3].

[1] Inouye SK. Delirium in older persons. N Engl J Med (2006) 354:1157-1165

[2] Lipowski ZJ Update on delirium. *Psychiatr Clin North Am* (1992) 15:335—346

[3] Leslie DL *et al.* One-year health care costs associated with delirium in the elderly population. *Arch Int Med* (2008) 168:27—32

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Older adults are known to be particularly vulnerable to the occurrence and effects of delirium when suffering an acute stress such as a medical illness or a hospitalization. The incidence of delirium in elderly hospitalized patients has been reported as ranging from 11 to 42% in general hospitalizations, and 15 to 62% in post-operative patients[4,5].

Treatment of the underlying illness is the current mainstay of treatment for delirium. Antipsychotic medications are widely used to manage the symptoms of delirium such as agitation and hallucinations. Side effects of these medications include over-sedation, prolonged QTc intervals, increased risk of potentially fatal cardiac arrhythmias, and extrapyramidal symptoms. There are currently no medications approved for the prevention of delirium in at risk patients.

Role of melatonin in delirium

Melatonin is a neurohormone synthesized from tryptophan and secreted by the pineal gland in a circadian pattern governed by the light-dark cycle.[6] It is known as an important mediator of the sleep-wake cycle.[7] Because disturbance of the sleep wake cycle is a core feature of delirium, it has been hypothesized that melatonin may play a role in the pathogenesis of delirium[8,9].

Both serum daytime levels and nocturnal peaks of melatonin have been shown to decrease progressively with age.[10,11] Additionally, both serum[12] and CSF[13] levels of melatonin have been shown to be markedly reduced in patients with Alzheimer's dementia, compared to controls. Levels of both serum melatonin and its urinary metabolites[14] have been demonstrated to differ in patients with delirium as compared to non-delirious controls[15,16,17].

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[4] Fong TG *et al.*Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol* (2009) 5:210—220

[5] Miller MO. Evaluation and management of dementia in hospitalized older patients. *Am Fam Physcian* (2008) 11:1265—1270

[6] Claustrat B, *et al.* The basic physiology and pathophysiology of melatonin. *Sleep Med Reviews* (2005) 9:11—24

[7] Brzezinski A. Melatonin in humans. *NEJM* (1997) 336:186—195

[8] Lewis MC and Barnett SR. Postoperative delirium: the tryptophan dysregulation model. *Med Hypotheses* (2004) 63:402—406

[9] de Jonghe *et al.* Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. *Int J Geriatr Psychiatry* (2010) 25:1201—1208

[10] Iguchi H, *et al.* Age-dependent reduction in serum melatonin concentrations in healthy human subjects. *J Clin Endocrinol Metab* (1982) 55:27—29

[11] Magri F, *et al.* Qualitative and quantitative changes of melatonin levels in physiological and pathological aging and in centenarians. *J Pineal Res* (2004) 36:256—261

[12] Kazuo M *et al.*Melatonin secretion rhythm disorders in patietns with senile dementia of Alzheimer's type with disturbed sleep-waking. *Biol Psych* (1999) 45:417—421

[13] Liu RY *et al.* Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoprotein E-epsilon 4/4 genotype. *J Clin Endocrinol Metab* (1999) 84:323—327

[14] Balan S, *et al.*The relation between the clinical subtypes of delirium and the urinary level of 6-SMT. *J Neuropsychiatry Clin Neurosci* (2003) 15:363—366

[15] Hidetaka S *et al.* Postoperative delirium and melatonin levels in elderly patients. *Am J of Surg* (2001) 182:449--454

[16] Yoshitaka S, *et al.* Perioperative plasma melatonin concentration in postoperative critically ill patients: its association with delirium. *J Crit Care* (2013) 28:236—242

[17] Sun, *et al*. Research of 24-hour dynamic sleep monitoring and melatonin changes in patients with delirium in intensive care unit. Chinese critical care medicine (2014) 10:726-729

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Melatonin for the prevention of delirium

Multiple case reports suggest that melatonin, given at a dose of 2 or 4 mg nightly is helpful in both prevention and management of delirium in both post-operative and non post-operative elderly hospitalized adults[18,19,20]. Several observational studies looking at the use of melatonin for the prevention of delirium, primarily in the ICU and post-operative settings, have supported the use of melatonin in the prevention of delirium. Ramelteon, a synthetic melatonin agonist, has been shown effective for the prevention of delirium in observational studies[21,22, 23] as well as in a randomized control trial[24].

Randomized Controlled Trials Studying Melatonin for Prevention of Delirium

A review of the literature revealed three randomized controlled trials to date that have looked at the use of melatonin for the prevention of delirium in elderly hospitalized patients. The results of these trials are summarized in the table below:

The trials outlined have yielded inconsistent results. While the Sultan and Al Aama studies both demonstrated decreased incidence of delirium in both medical and surgical patients treated with melatonin, the de Jonghe trial did not show a benefit to melatonin in the prevention of delirium.

A meta-analysis published in April, 2015, extracted data from the four studies described above, to consider the incidence of delirium in a total of 669 patients given prophylactic melatonin.[25] Melatonin was shown to decrease the incidence of delirium, with a RR of 0.41 (95% CI 0.15—1.13, p=0.08). In a subgroup analysis that looked at the elderly patients on medical (not surgical) services, use of prophylactic melatonin was shown to decrease the incidence of delirium by 75%, with a RR of 0.25 (95% CI 0.07—0.88, p=0.03), although no statistical difference was found in patients admitted to surgical service. A major limiting factor is the heterogeneity between these studies that looked at different patient populations, different doses, and used different scales to assess delirium. While the collective data is intriguing, further study is necessary in order to clarify the potential role of melatonin in the prevention of delirium in elderly hospitalized adults.

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[18] Hanania M, Kitain E. Melatonin for the treatment of and prevention of postoperative delirium. *Anesth Analg* (2002) 94:338—339

[19] Lammers M, Ahmed AI. Melatonin for sundown dyndrome and delirium in dementia: is it effective? *J Am Geriatr Soc* (2013) 61:1045—1046

[20] Panagiotis A, *et al.* Melatonin treatment in the prevention of postoperative delirium in cardiac surgery patients. *Polish J of Thoracic and Cardiovascular Surgery* (2015) 12:126—133

[21] Motohide F *et al.* Marked improvement in delirium with ramelteon: five case reports. *Psychogeriatrics* (2012) 12:259--262

[22] Akihiro T *et al.* Ramelteon for the treatment of delirium in elderly patients: a consecutive case series study *Int J Psych in Medicine* (2014) 47:97—104

[23] Ohta T, *et al.*Melatonin receptor agonists for treating delirium in elderly patients with acute stroke. *J Stroke Cerebrovasc Dis.* (2013) 22:1107—1110

[24] Hatta K *et al.* Preventive effects of ramelteon on delirium; a randomized placebo controlled trial. *JAMA Psychiatry* (2014) 71:397—403

[25] Chen S, *et al.* Exogenous melatonin for delirium prevention: a meta-analysis of randomized controlled trials. *Mol Neurobiol* (2015)

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Lead author/year	Sultan, 2010[26] (single center double blinded RCT)	Al-Aama, 2011[27] (Single center double blinded RCT)	de Jonghe, 2014[28] (multicenter, double-blinded RCT)
Setting	Post-op patients > 64, following hip arthroplasty	Pts > 64, admitted to IP internal med service	Patients > 64 admitted for acute hip surgery
Definition of delirium	AMT (abbreviated mental test) < 8	CAM (confusion assessment method) (delirium as defined by Memorial Delirium Assessment Scale was a secondary outcome)	DSM IV; Delirium observation screening scale was completed per each nursing shift
Intervention	Group 1—no premedication Group 2—5 mg melatonin nightly, + 5 mg 90 min prior to operation Group 3—7.5 mg Versed nightly and 90 min prior to operation Group 4—100 mg clonidine nightly and 90 min prior to operation	Group 1—0.5 mg melatonin qHS Group 2—placebo Intervention continued until DC, death, or 14 days	Group 1—3 mg melatonin q HS Group 2—placebo Treatment continued x 5 days
Exclusion criteria	Hx EtOH abuse Sensory impairment Dementia Severe anemia or infection IC event Fluid/lyte disturbance Acute cards or pulm event On anticonvulsants, antidepressants, antihistamines, antiparkinsonian agents, antipsychotics, or benzos	Expected stay/life expectancy < 48 hours Non-English speaking Unable to take oral meds Hx IC bleed or seizure Hx non-therapeutic INR on Coumadin Allergy to melatonin	Delirium at time of enrolment Transfer from OSH Already on melatonin Unable to speak Dutch
Results	N=222 Control group—32.65% post-op delirium Melatonin group—9.43% post-op delirium (p=0.003) (44% in Versed group, 37.25 in clonidine group)	N=122 12% of pts in treatment group developed delirium, compared to 31% in placebo group	N=378 29.6% of patients in melatonin group developed delirium v 25.5 in the placebo group
Notes	-AMT initially designed to detect cognitive impairment, not delirium	No statistically significant difference in delirium as measured by MDAS	-melatonin group had statistically shorter duration of delirium -had 3 mo follow up to assess cognitive function and mortality rates (no difference)

[26] Sultan SS, *et al.* Assessment of the role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. *Saudi J Anaesth* (2010) 4:169—173

[27] Al-Aama T, *et al.* Melatonin decrease delirium in elderly patients: a randomized placebo-controlled trial. *Int J Geriatr Psychiatry* (2011) 26:687—694

[28] de Jonghe, *et al.* Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. *CMAJ* (2014) 186:547—556

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3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

   This study will be a randomized controlled trial, designed to evaluate the efficacy of melatonin in decreasing the incidence of delirium in elderly hospitalized adults. The study will be conducted on four general Internal Medicine inpatient services at Yale-New Haven Hospital, St. Raphael's campus, Verdi 4 West, Verdi 5 North, Celantano 4, and Celantano 3. Randomization will be accomplished with the assistance of the Yale Investigative Drug Service Pharmacy. They will be using a randomization generator with active/placebo on a 1 to 1 basis in randomly permutated blocks of 4

   Within 24 hours of admission to the inpatient floor, study subjects will be approached by a member of the research team, and asked for informed consent. Patients that consent to participate and meet our inclusion criteria will be ordered the appropriate study drug by the floor pharmacist, per the Yale Investigative Drug Service's randomization to either the treatment or the placebo arm. Each subject will be ordered a capsule containing either placebo (cellulose microcrystylline) or 5 mg melatonin each evening at 9 p.m. The study drug can be given as early as 7pm on the day of admission, if necessary, to allow treatment to begin within 24 hours of admission to the floor.. The capsules will be prepared and administered by the Yale-New haven Hospital Investigational Drug Service. The capsules will be administered nightly until discharge or a maximum of 2 weeks if the hospitalization is prolonged. The capsule must be swallowed whole and not opened.
   Subjects will be assessed twice daily, once in the- a.m. and again in the p.m by the floor nurses for evidence of delirium using the Short CAM (Confusion Assessment Method), which is a validated clinical tool for identifying delirium, and the current standard of practice tool for the diagnosis of delirium. This evaluation should take maximally 5 to 10 minutes to complete.
   While it is considered standard of care for nurses to administer the Short CAM once daily at Yale-New Haven Hospital, the twice daily Short CAM is standard of care at the University of Connecticut Hospital but not currently at the Yale-New Haven Health System with the exception of Verdi 4 West where the CAM is administered twice a day for all patients.
   The primary endpoint will be the occurrence of delirium as defined by the Short CAM by the time of discharge or prior to hospital day 15, whichever occurs first. The study drug will be continued until the primary end point of delirium is reached, discharge or hospital day 15. The maximum period of study drug administration will be 14 days. If the patient's length of stay exceeds 14 days the patient's participation in the study will end and the subject will be recorded as having completed the study without delirium. If the primary end point of delirium is reached, the subject will have completed the study, participation will be over and the study drug will no longer be administrated.

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While causes of delirium will be extracted from the chart, all investigations will be done by the primary inpatient team. The diagnosis of delirium will be communicated to the inpatient team.

Patients that agree to participate in the study will not be prescribed melatonin as a sleeping aid. All care, including medications for sleep and management of delirium will be per standard of care, as decided by the attending physician of record. If the primary team believes that melatonin is medically indicated the patient will not be enrolled or be withdrawn from the study.

4. **Genetic Testing N/A** ☒
   A. Describe
      i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
      ii. the plan for the collection of material or the conditions under which material will be received
      iii. the types of information about the donor/individual contributors that will be entered into a database
      iv. the methods to uphold confidentiality

   B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
   C. Is widespread sharing of materials planned?
   D. When and under what conditions will materials be stripped of all identifiers?
   E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
      i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

   F. Describe the provisions for protection of participant privacy
   G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

   The study will recruit subjects ≥ age 65, who are admitted to the four participating general internal medicine floors at St. Raphael's hospital.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

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☐ Children	☒ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☒ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

If patients are not competent to sign the informed consent, we will contact the healthcare proxy to provide informed consent for enrollment.

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria

- Age ≥ 65
- Inpatient admission to general internal medicine service

Exclusion Criteria

- Expected lifespan or length of stay ≤ 48 hours
- Non-English speaking
- Already taking melatonin at the time of randomization (at least one dose taken in the prior week)
- Already taking ramelteon (Rozerem) at the time of randomization (at least one dose taken in the prior week)
- Presence of delirium at the time of randomization
- Unable to take oral medications
- Subject or proxy unable to provide informed consent
- Unable to give consent within 18 hours of invitation or within 24 hours of being admitted to the medical floor
- Known allergy to melatonin
- Patients taking warfarin, nifedipine and fluvoxamine
- Patients with severe liver impairment (admission diagnosis of active liver disease such as cirrhosis or acute hepatitis)
- Unable to recall at least 2 of 3 words after distraction by asking the subject to name the days of the week backwards starting with Sunday.

8. How will **eligibility** be determined, and by whom?

A member of the research team will use the hospital EMR to screen admissions to the four participating general Internal Medicine floors for eligibility, based on the above inclusion and exclusion criteria. This will be accomplished via the OnCore and YCCI EPIC Support Services. The consent process will include a brief description of the study with an

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explanation that the subject may receive no direct benefit from participating but patient care may in general improve if the study drug successfully prevents delirium. If the patient is interested in enrolling then the patient is asked to remember 3 words (apple, penny, and table) and then is distracted by being asked to recite the days of the week backwards starting with Sunday. If the subject can remember at least 2 of the 3 words then the entire consent in reviewed in depth and the subject is asked if he understands and if he has any questions before signing. A "teach back" will be accomplished to insure that the subject or the surrogate understands all the research aspects of the study A Short CAM will then be performed by the investigator to evaluate for delirium. If delirium is not diagnosed via the Short CAM, the consent form will be completed and the patient entered into the trial.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Minimal risks are anticipated with this study however participation in the study may involve risks that are currently not know. Possible risks include the swallowing of an extra pill and the lack of ability to take melatonin for impaired sleep. While Micromedex lists side effects of melatonin, such as tachyarrhythmia, red/flushed skin, hypothermia, decreased glucose tolerance, abdominal cramps/diarrhea, confusion, decreased reaction time, sedation, sleep pattern disturbance, and worsening of depression, these are considered rare and usually with little clinical effect. A recent review in the journal Clinical Drug Investigations (Andersen LP, Gögenur I, Rosenberg J, Reiter RJ. Clin Drug Investig. 2016 Mar;36(3):169-75. doi: 10.1007/s40261-015-0368-5. PMID:26692007) concluded that the short-term use of melatonin is safe, even in extreme doses and that only mild adverse effects have been reported and are probably no different than placebo[29], with the possible exception of sleepiness. Other potential adverse effects include dizziness, headache, and nausea as described below, in section VI.2.
Melatonin should have no major drug interactions or effects on other possible drug interventions in our subjects. Mild to moderate interactions with warfarin, nifedipine and fluvoxamine are noted in Micromedex and patients treated with these medications will not be included in the study.

Another possible risk involves potential breach of confidentiality with the collection of protected patient information. All patients in the study will be initially de-identified by use of medical record number and subsequently further de-identified by receiving a study number. Paper records will be kept in a locked office and computerized records will be kept in a secure hospital computer.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Regarding the lack of ability to take melatonin for sleep; this risk is minimal, as melatonin is rarely used as a sleeping aid on the participating services. Currently only 7.2% of patients admitted to Celantano 3 and 12.3% of patients admitted to V4 West receive melatonin for

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sleep. Clinicians will continue to treat insomnia with the usual non-pharmacologic and pharmacologic methods.

All patient data will be logged in a password protected YCCI / OnCore grid that will only be accessed by study personnel. All participants in the study will be HIPAA and HSPT trained.

The investigation team will review all patients, in EPIC or in persontwice per day. Any possible complications will be followed closely.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

       There is minimal risk anticipated for subjects participating in this study. Melatonin is considered a safe, over-the-counter, non-prescription supplement. A recent review[29] concluded that "Melatonin is safe for short-term use, even when given in extreme doses. Mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported in levels corresponding to placebo treatments." Section 9 lists Micromedex's side effect profile.

    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?

       Not applicable

    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for

       The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency on a monthly basis. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

       The principal investigator or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

       This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. In the unlikely event that such events occur, Reportable Adverse Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to

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the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project through regular study meetings.

d. For multi-site studies for which the Yale PI serves as the lead investigator:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
   ii. What provisions are in place for management of interim results?
   iii. What will the multi-site process be for protocol modifications?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.
13.

Primary Outcome:
Incidence of delirium per admission of medical geriatric patients
Incidence of delirium per patient days of hospitalization in medical admission of geriatric patients

Secondary outcomes:
Risk factors associated with incident delirium
Duration of delirium by study group
Hospital length of stay

Sample size based was estimated using openepi.com (similar results with Stata version 14 sample size calculator) based on control group incidence of delirium in medical subgroup of 30%. (Chen et al: Exogenous melatonin for delirium prevention: a meta-analysis of randomized controlled trials - Molecular Neurobiology online publication 21 July 2015) with relative risk reduction of 30 %.

Sample Size:X-Sectional, Cohort, & Randomized Clinical Trials

Two-sided significance level(1-alpha):	95
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	1
Percent of Unexposed with Outcome:	30
Percent of Exposed with Outcome:	21
Risk/Prevalence Ratio:	0.7
Risk/Prevalence difference:	-9

Sample size estimation by the Fleiss method yielded a total sample size of 734 with 367 in each group.

Descriptive statistics such as percentages for binary categorical variables, means and standard deviations for continuous variables. Fisher's exact test or chi-square test will be used to compare categorical variables. For continuous variables we will use t-test of unequal variances for means for normally distributed variables and the Wilcoxon-Mann-Whitney where normal distribution cannot be assumed. Risk ratio will be calculated using Stata statistical program version 14. (StataCorp **LP,** 4905 Lakeway Drive, College Station, Texas) Associations with covariates will be tested using logistic regression with presence of incident delirium as the dependent variable.

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Person days to delirium will be compared between the two groups using Survival analysis with Kaplan Meier curves, logrank test and Cox proportional hazards (covariates include age, comorbidities, medication numbers, presence of risk factors for delirium – polypharmacy, use of psychotropic or sedating medications, and use of bladder catheters).

Upon completing enrollment and analysis of 367 subjects, Dr. Donna Windish, a independent statistical expert, will analyze the data. In addition, an independent geriatrician expert in delirium will review any equivocal CAM results and make a decision as to the occurance of delirium.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Melatonin—FDA categorized as a dietary supplement for sleep aid

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?

FDA IND 129224-Melatonin

b. Who holds the IND?

Dr. Stephen Atlas

c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

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Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☐ Yes ☐ No
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☐ Yes ☐ No
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☐ Yes ☐ No
iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☐ Yes ☐ No
v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☐ Yes ☐ No

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):
- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might

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influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Melatonin is categorized by the FDA as a dietary supplement and is currently in use over the counter and ordered in a small percentage of hospitalized patients as a sleep aid. Side effects of melatonin are rare and mild; documented adverse effects to melatonin include dizziness, headache, nausea, and sleepiness. With the exception of sleepiness these are similar in incidence to placebo. The half-life of melatonin is 30 to 50 minutes. There have been no studies to date that have documented any serious adverse effects related to short or even long term use of melatonin.[29] Melatonin is taken orally. Because it is categorized as a dietary supplement and not a drug, it is marketed over the counter, and there is no recommended dose. It is marketed in doses ranging from 0.5 to 10 mg. See section 9, Risks, for all the possible side effects as listed in Micromedex.

3. **Source:** a) Identify the source of the drug or biologic to be used.
The Yale Investigational Drug Service Pharmacy

b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
If yes, by whom?

Per the Department of Medicine Research Grant funding

3. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
No special storage or preparation will be required.

Check applicable Investigational Drug Service utilized:

☒ **YNHH IDS**	☐ **Yale Cancer Center**
☐ **CMHC Pharmacy**	☐ **West Haven VA**
☐ **PET Center**	☐ **None**
☐ **Other:**	

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

4. **Use of Placebo:** ☐ **Not applicable to this research project**
If use of a placebo is planned, provide a justification which addresses the following:
a. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.

There are currently no approved therapies for the prevention of delirium.

[29] Andersen, L. P., Gogenur, I., Rosenberg, J., & Reiter, R. J. (2015). The Safety of Melatonin in Humans. *Clin Drug Investig*. doi: 10.1007/s40261-015-0368-5

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b. State the maximum total length of time a participant may receive placebo while on the study.

2 weeks

c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.

There is no potential harm associated with use of placebo except as noted in section 9. The placebo will be prepared by the Yale Investigational Drug Service and will consist of cellulose microcrystalline in a capsule

d. Describe the procedures that are in place to safeguard participants receiving placebo.

Each patient will be observed in the hospital by the research team and any complications will be noted. If the patient cannot swallow without compromise then they will be removed from the trial.

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings.*

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☒ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☐ No If no, explain why this is acceptable.

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol: 734
   (367 patients in the treatment and 367 patients in the placebo group)

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☐ Flyers ☐ Internet/Web Postings ☐ Radio

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☐ Posters ☐ Mass E-mail Solicitation ☐ Telephone
☐ Letter ☐ Departmental/Center Website ☐ Television
☒ Medical Record Review ☐ Departmental/Center Research Boards ☐ Newspaper
☐ Departmental/Center Newsletters ☐ Web-Based Clinical Trial Registries
☐ YCCI Recruitment database ☐ Clinicaltrials.gov Registry (do not send materials to HIC)
☒ Other (describe): subjects that meet inclusion criteria will be approached by a member of the research team upon admission to the hospital and recruited for the study.

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Utilizing OnCore and it's EPIC Support Team, a member of the research team will screen the list of admitted patients to the participating services daily to identify all new admissions who are appropriate candidates to enter the study. The electronic chart will then be reviewed to determine if the potential subjects meet all eligibility criteria and if concern for discharge within 48 hours is an issue then the primary treating team will be approached for their prediction/plan.

b. Describe how potential subjects are contacted.

They will be approached on the medicine floor to which they are admitted by a member of the research team Within 24 hours of admission.

c. Who is recruiting potential subjects?

All listed member of the research team will be responsible for recruiting potential subjects. Additionally, after submitting the appropriate HIPAA and research training course documentation and with the individual specific approval of the Human Investigation Committee, other recruiters may be trained by the team.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☐ Yes ☒ No
b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:
☐ Names
☐ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

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☐ Telephone numbers
☐ Fax numbers
☐ E-mail addresses
☐ Social Security numbers
☒ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☒ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers, including license plate numbers
☐ Device identifiers and serial numbers
☐ Web Universal Resource Locators (URLs)
☐ Internet Protocol (IP) address numbers
☐ Biometric identifiers, including finger and voice prints
☐ Full face photographic images and any comparable images
☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☒ Yes, some of the subjects
☐ No

If yes, describe the nature of this relationship.

Several members of the research team may be working as either the resident or attending physician for the study subjects at the time of data collection. The Yale Investigational Drug Service will be doing the randomization so that all will remain blinded as to the treatment arm and the placebo arm.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment purposes only
☐ For inclusion of non-English speaking subject if short form is being used

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data; The patients' names who are admitted to Celantano 3, Celantano 4, Verdi 5 North, and Verdi 4 West and fit our inclusion criteria will be sent to the investigators via OnCore / EPIC. Before interviewing the patient we will need to review our exclusion criteria which can be done both via EPIC chart review and with discussion with the primary team. Once we are comfortable

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that the patient is a candidate for inclusion we will interview the patient and further review the inclusion and exclusion criteria and begin the invitation to consider participating in the study. By reviewing the chart and perhaps interviewing the care team we will avoid needlessly bothering some patients and be more efficient in our recruitment process.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data; In the event that a patient does not understand and/or cannot explain back to the investigator seeking informed consent, what the study entails, but does give us his/her affirmative assent, we will seek out the LAR, in person or by phone, to obtain a surrogate consent.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accou nting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   ☒ Compound Consent and Authorization form
   ☒ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.
9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Potential subjects will be approached by a member of the research team within 24 hours of their admission to the hospital. Care will be taken to explain the purpose of this study as well as potential risks associated with participation. If the subject wishes to proceed then the full consent form will be explained, and the potential subject will have opportunity and time to read the consent document on their own.

Given our elderly subject population, we anticipate that a percentage of our subjects will have cognitive deficits that will render them unable to provide their own informed consent. In those cases, in addition to requiring the subject's affirmative assent, the medical decision maker of record will be approached for informed consent. In such cases, the medical decision maker will be approached in person, if possible. If this is not possible, telephone consent witnessed and signed

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by a member of the medical staff will be obtained.. The consent will be faxed to the surrogate if possible. All surrogates who give consent and are available to come to the hospital will be reconfirmed with written consent as soon as possible.
All subjects will be evaluated by the investigative team twice daily as long as they remain in the study. If subjects regain their capacity to give consent, such consent will be mandatory to their continuing in the study.
Consent must be obtained within 18 hours of the invitation to participate for the subject to be entered into the trial.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

    During the consent process, subjects will be asked to describe their understanding of the study, and given an opportunity to ask questions. If the investigator concludes that a subject lacks the capacity to consent, the medical decision maker of record will be approached for consent after the subject gives his/her affirmative assent..

11. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

    The subjects will receive the compound authorization and consent to enter the Melatonin to Prevent Delirium Study
    that will be reviewed by the study team personnel.

12. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

    Non-English speaking subjects will not be included in the study

    12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
    YES ☐ NO ☒
    (not applicable)

    Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

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Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ **Not requesting a consent waiver**

☒ **Requesting a waiver of signed consent (to obtain verbal consent from LAR, if not available)**

☒ **Requesting a full waiver of consent (to access medical records for recruitment purposes)**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6)**

☒**Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes ☒ No

b. Does a breach of confidentiality constitute the principal risk to subjects?

☒ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity

☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

☒ **Requesting a waiver of signed consent for the Entire Study** (Note that an information sheet may be required.) (to obtain verbal consent via telephone from the LAR, if not available)

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes ☒No

b. Does a breach of confidentiality constitute the principal risk to subjects?

☒Yes ☐ No

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OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☒ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

B. **Full waiver** of consent: (No consent from subjects will be obtained for the activity.)

☒ **Requesting a waiver of consent for Recruitment/Screening only (to access medical records for recruitment purposes)**

a. Does the research activity pose greater than minimal risk to subjects?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity

☒ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☒ No

c. Why would the research be impracticable to conduct without the waiver? The patients' names who are admitted to Celantano 3,Celantano 4, Verdi 5 West and Verdi 4 West and fit our inclusion criteria will be sent to the investigators via OnCore / EPIC. Before interviewing the patient we will need to review our exclusion criteria which can be done both via EPIC chart review and with discussion with the primary team. Once we are comfortable that the patient is a candidate for inclusion we will interview the patient and further review the inclusion and exclusion criteria and begin the invitation to consider participating in the study. By reviewing the chart and perhaps interviewing the care team we will avoid needlessly bothering some patients and be more efficient in our recruitment process.

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? N/A

☐ **Requesting a full waiver of consent for the Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.) N/A**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***

☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

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a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

- Medical record number
- Date of Admission
- hyperactive delirium
- hypoactive delirium
- Length of stay
- Age
- Gender
- Primary diagnosis
- Secondary diagnosis
- Mortality
- Use of rstraints
- # prn antipsychotic doses
- PRN sleep meds
- Placement of foley catheter
- Result of daily CAM assessment

b. How will the research data be collected, recorded and stored?

Research data will be collected and recorded on a password protected Microsoft Excel spreadsheet that will only be accessible to study investigators via OnCore

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☐ Laptop Computer ☐ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

Data will be stored on a password-protected computer only (Yale-New Haven Hospital network server accessed by password only via OnCore). All data will be coded and a masterlist linking the subject identifiers to the coded research data will be kept in a locked location in the hospital, separate from the research data.

Do all portable devices contain encryption software? ☐ Yes N/A—portable devices will not be used to collect data

If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

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Once the research is completed, all subject data will be deleted from the secure server.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

The research team will have access to deindentified confidential protected health information.

g. If appropriate, has a Certificate of Confidentiality been obtained?

NA

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

NA

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Delirium is a common problem in hospitalized adults with a high degree of associated morbidity, prolonged length of hospital stay, and increased healthcare costs. Currently, there are no interventions approved for the prevention of delirium. Current medical options for managing delirium such as antipsychotic drugs are associated with their own morbidity, including cardiac arrhythmias and oversedation. Melatonin, a supplement used for sleep with an excellent safety profile, may have the potential to dramatically decrease rates of delirium in hospitalized adults. Direct benefits for patients in our study are unknown and subjects may not directly benefit from participation.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

Not to participate in the study.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

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None

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   None

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.

   No more than minimal risk is involved.

a. Will medical treatment be available if research-related injury occurs?
   Yes, during the same hospitalization period.

c. Where and from whom may treatment be obtained?
   From the medical team caring for the patient during the admission.

d. Are there any limits to the treatment being provided?
   We do not expect so, but will defer to the primary medical team caring for the patient.

e. Who will pay for this treatment?
   The patient's insurance company, or the patient.

f. How will the medical treatment be accessed by subjects?
   The medical treatment will be available during the hospitalization, and the PI will notify the primary medical team, as appropriate.

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