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The Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) study: Protocol for an International Multicenter Randomized Controlled Trial

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The Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) Study: Protocol for an International Multicenter Randomized Controlled Trial

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WORLD HEALTH ORGANIZATION DATA SET

Primary Registry and Trial Identifying Number	ClinicalTrials.gov: NCT01690988
Date of Registration in Primary Registry	August 7, 2012
Secondary Identifying Numbers	IRB ID#: 201206071
Source(s) of Monetary or Material Support	Department of Anesthesiology, Washington University School of Medicine in St. Louis Departments of each respective site
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Secondary Sponsor(s)	Department of Anesthesiology, University of Michigan Medical School in Ann Arbor
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Public Title	The Prevention of Delirium and Complications After Surgical Treatment (PODCAST) Study
Scientific Title	The Prevention of Delirium and Complications After Surgical Treatment (PODCAST) Study: a randomized controlled trial
Countries of Recruitment	United States, Canada, Switzerland, India, South Korea

Health Condition(s) or Problem(s) Studied	Postoperative delirium, postoperative pain, and postoperative nausea and vomiting
Intervention(s)	Study arm 1: 0.5 mg/kg of ketamine diluted to 20 mL with saline given intravenously after anesthetic induction and before surgical incision. Study arm 2: 1 mg/kg of ketamine diluted to 20 mL with saline given intravenously after anesthetic induction and before surgical incision Placebo: 20 mL of saline solution given intravenously after anesthetic induction and before surgical incision.
Key Inclusion Criteria and Exclusion Criteria	Ages eligible for study: ≥ 60 years Sexes eligible for study: both Healthy volunteers: no Inclusion criteria: patients 60 years or older undergoing major open surgery receiving general anesthesia Exclusion criteria: allergy to ketamine, pheochromocytoma, aortic dissection, intracranial hemorrhage, intracranial mass, history of hypertensive emergency, uncontrolled glaucoma, history of drug misuse (e.g., ketamine, cocaine, heroin, amphetamine, methamphetamine, MDMA, phencyclidine, lysergic acid, mescaline, psilocybin), currently taking anti-psychotic medications (e.g., chlorpromazine, clozapine, olanzapine, risperidone, haloperidol, quetiapine, paliperidone, amisulpride, sertindole), weight <50 kg (110 lbs) or >200 kg (440 lbs).
Study Type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double blind (subject, healthcare providers, investigator, research personnel) Assignment: single arm Primary purpose: prevention Phase III
Date of First Enrollment	February 2014

Target Sample Size	600
Recruitment Status	Recruiting
Primary Outcome(s)	Outcome name: postoperative delirium Method of measurement: Confusion Assessment Method or Confusion Assessment Method for the ICU Timepoints of interest: two hours post-operation, mornings and evenings of postoperative days one through three
Key Secondary Outcomes	Outcome name: postoperative pain Method of measurement: Visual Analog Scale and Behavioral Pain Scale or Behavioral Pain Scale – Non-Intubated Timepoints of interest: two hours post-operation, mornings and evenings of postoperative days one through three Outcome name: postoperative nausea and vomiting Method of measurement: patient self-report as present or absent and degree of severity (mild, moderate, or severe). Timepoints of interest: two hours post-operation, mornings and evenings of postoperative days one through three

ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

Principal Investigators:
Michael Avidan, MBBCh
George Mashour, MD, PhD

Responsibilities include: design and conduct of PODCAST trial, preparation of protocol and revisions, organizing steering committee meetings, and publication of study reports.

Steering Committee:

Michael Avidan, MBBCh	Eric Jacobsohn, MBBCh	Kane Pryor, MD
Daniel Emmert, MD, PhD	Hilary Grocott, MD	Gyujeong Noh, MD, PhD
Robert Veselis, MD	Stephen Choi, MD	Paul Pagel, MD, PhD
Sharon Inouye, MD, MPH	Ryan Pong, MD	Judith Hudetz, PhD
George Mashour, MD, PhD	Virendra Kumar Arya, MD	Milo Engoren, MD
Robert Downey, MD	Heiko Kaiser, MD	

Responsibilities include: agreement of final protocol, recruitment of patients and coordinating with principle investigator, reviewing progress of study and if necessary, changes to the protocol.

Trial Management Committee:
Michael Avidan, MBBCh
George Mashour, MD, PhD
Hannah Maybrier

Responsibilities include: study planning, organization of steering committee meetings, provides annual risk report to the Human Research Protection Office at Washington University, reports SAEs (Serious Adverse Events) to Washington University IRB (Institutional Review Board), responsible for maintenance of electronic database, REDCap, advice for lead investigators, assistance with international review, ethics committee applications, data verification, and randomization of study participants

Lead Investigators:

Michael Avidan, MBBCh	Eric Jacobsohn, MBBCh	Kane Pryor, MD
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George Mashour, MD, PhD	Virendra Kumar Arya, MD	Milo Engoren, MD
Robert Downey, MD	Heiko Kaiser, MD	

Responsibilities include: identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol.

Data and Safety Monitoring Committee:
Arbi Ben Abdallah, PhD
Michael Avidan, MBBCh
Charlie Hantler, MD
Simon Haroutounian, PhD

Responsibilities include: reviewing and evaluating the study data to ensure participant safety, study conduct, progress, and efficacy, and making recommendations regarding the continuation, modification, and termination of the trial.

PROTOCOL VERSIONS

June 18, 2012 Original

April 25, 2013 Amendment 01: Changes to study aims:

- Changed specific aim 1: removed associated adverse events, such as ICU stay, hospital stay, and mortality
- Changed specific aim 2: removed assessing symptoms of other chronic neuropsychiatric processes (such as depression and posttraumatic stress).
- Changed specific aim 3: testing the effects of ketamine on postoperative depression and stress to attenuating postoperative inflammation.

Amendment 02: Addition of study arm. Patients are randomized to one of three study arms: 0.5 mg/kg ketamine, 1 mg/kg ketamine, or placebo dose of equal volume

Amendment 03: Removed phrase that patients will be contacted between 1 and 3 months after surgery to ask about quality of life, lasting pain, feelings of depression or stress.

Amendment 04: Removed phrase that patients will be contacted 1 year after surgery to ask about quality of life and mental function.

Amendment 05: Changed inclusion criteria to patients older than 60 years (was 65 years)

Amendment 06: Removal of phrase regarding study of ketamine use with posttraumatic stress disorder.

Amendment 07: Addition of phrase that hypothesis is based on published data of reduced pain and opioid consumption after surgery. The study will resolve gap in the field by further assessing chronic pain

Amendment 09: Addition of phrase that discusses delirium and pain as two adverse and potentially linked outcomes that have not been previously jointly evaluated in a large clinical trial.

May 30, 2013 Amendment 01: Removal of specific aim 3: testing whether ketamine improves postoperative inflammation

January 3, 2014 Amendment 01: Addition of weight criterion to Exclusion Criteria; weight < 50 kg (110 lb.) and > 200 kg (440 lb.) are excluded.

Amendment 02: Addition of justification of sample size. Included statement that when assuming a two sided type one error of 5% the sample size of 600 patients will detect decrease in delirium from

25% to 15% with the use of ketamine with a power greater than 80%.

Amendment 03: Change in randomization protocol. We will not randomize cardiac and non-cardiac surgery patients separately.

Amendment 04: Omission of one of the points of clarification of the pilot study – to determine the efficacy of ketamine in cardiac vs. non-cardiac surgery.

Amendment 05: Changes to baseline assessments. Addition of Confusion Assessment Method (CAM), Behavioral Pain Scale – Non-Intubated (BPS-NI), Visual Analog Scale (VAS), Barthel Index, Patient Health Questionnaire-8 (PHQ-8), STOP-Bang, and questions about falls.

Amendment 06: Addition of medical record review screening for comorbid conditions included in the Charlson Comorbidity Index and lab values including electrolytes and blood counts.

Amendment 07: Addition of the statement that clinicians are instructed not to give enrolled patients ketamine as part of their anesthetic technique.

Amendment 08: Addition of mailed survey sent 30 days postoperatively assessing depression, positive and negative affect, quality of life, functional independence, and pain using the PROMIS v1.0 – Emotional Distress – Depression, Positive and Negative Affect Scale (PANAS), Veteran's Rand-12 (VR-12), Barthel Index, and the Brief Pain Inventory Short Form (BPI-SF), respectively.

Amendment 09: Addition of Family Confusion Assessment Method (FAM-CAM) at Washington University, a tool in which family members will assess patient's behavior and determine if delirium is suggested.

Amendment 10: Addition of observational tools used to assess pain: BPS, BPS-NI

Amendment 11: Addition of postoperative nausea and vomiting as a secondary outcome.

Amendment 12: Addition of description of delirium assessment training.

Amendment 13: Addition of statement that REDCap (Research Electronic Data Capture) will be used.

Amendment 14: Addition of statement saying there are no planned interim analyses.

Amendment 15: Changes in statistical analysis:

- Cox proportional-hazards model for recurrent events used to determine the effects of low-dose ketamine on the occurrence and duration of delirium across study groups.
- Poisson hurdle regression used to determine the differences in patients with delirium and those without delirium, and the differences in recurrence in the patient population that does experience delirium.
- Both Poisson and Cox will also be used to compare effects of ketamine on cardiac vs. non-cardiac surgery patients.
- Cochran-Armitage test to determine dose-response trends
- Mixed-effects regression model to detect differences of continuous outcome variables in subgroups.

Amendment 16: Addition of list of short- and long-term side effects of ketamine

March 7, 2014

Amendment 01: Addition of Patient Health Questionnaire 8 (PHQ 8) for baseline assessments and postoperative day three assessments. This replaced the PROMIS depression screen. We would like to assess depression using the same tool at all time points.

Amendment 02: Collection of patient's email at baseline. Patients have the option to receive the 30 day survey by mail or email.

Amendment 03: Addition of Figure 1: Study Flow Chart. This is a visual representation of study conduct.

ABSTRACT

Introduction: Postoperative delirium is one of the most common complications of major surgery, affecting 10-70% of surgical patients 60 years and older. Delirium is an acute change in cognition that manifests as poor attention and illogical thinking, and is associated with longer ICU and hospital stay, long-lasting cognitive deterioration, and increased mortality. Ketamine has been used as an anesthetic drug for over 50 years and has an established safety record. Recent research suggests that, in addition to preventing acute postoperative pain, a sub-anesthetic dose of intraoperative ketamine could decrease the incidence of postoperative delirium as well as other neurologic and psychiatric outcomes. However, these proposed benefits of ketamine have not been tested in a large clinical trial.

Methods: The PODCAST study is an international, multicenter, randomized controlled trial. Six hundred cardiac and major non-cardiac surgery patients will be randomized to receive ketamine (0.5 mg/kg or 1 mg/kg) or placebo following anesthetic induction and prior to surgical incision. For the primary outcome, blinded observers will assess delirium on the day of surgery (postoperative day 0) and twice daily from postoperative days 1 to 3 using the Confusion Assessment Method or the Confusion Assessment Method for the ICU. For the secondary outcomes, blinded observers will estimate pain using the Behavioral Pain Scale or the Behavioral Pain Scale for Non-Intubated Patients and patient self-report.

Ethics and dissemination: The PODCAST trial has been approved by the ethics boards of five participating institutions; approval is ongoing at other sites. Recruitment began in February 2014 and is expected to continue through 2015. Dissemination plans include

presentations at scientific conferences, scientific publications, stakeholder engagement and popular media.

Registration details: The study is registered at clinicaltrials.gov, NCT01690988 (last updated December, 2013).

The PODCAST trial is being conducted under the auspices of the Neurological Outcomes Network for Surgery (NEURONS).

STRENGTHS:

- The effects of ketamine are being observed in the routine clinical setting.
- Because PODCAST is a multicenter international trial, the results of the study will potentially be generalizable.
- This trial has a novel focus of assessing delirium and pain concurrently. Results could reveal that these two outcomes are potentially linked in the postoperative setting.
- PODCAST is a randomized, controlled double-blinded study.
- Investigators assessing for delirium have been appropriately trained and will use reliable and validated assessment tools.

LIMITATIONS:

- Pain is a subjective experience and is therefore difficult to measure.
- The Visual Analog Scale (VAS) is not a validated pain assessment instrument in delirious patients. In an attempt to mitigate this limitation, pain will also be assessed

observationally using the Behavioral Pain Scale (BPS) and the Behavioral Pain Scale – Non-intubated (BPS-NI).

- Delirium is fluctuating in nature. Because patients will be assessed at discrete time points, it is possible that some episodes of delirium will not be detected.

INTRODUCTION

Background and rationale

Delirium

Postoperative delirium is one of the most common complications of major surgery and affects between 10% and 70% of all surgical patients older than 60 years (Table 1).[1] The estimated additional healthcare costs associated with delirium exceed $60,000 per patient per year.[2] While causal relationships have not been established, delirium is associated with increased morbidity and mortality, prolonged length of hospital and intensive care unit (ICU) stay, functional and cognitive decline with nursing home or long-term care facility placement.[3-6] Furthermore, the acute deterioration in cognition and psychomotor agitation frequently seen with delirium is often distressing for both patients and their families.

Surgery type	Study (year)	Population	Delirium Rate	Detection method
Unselected	Radtke[7]	Recovery room after elective general anesthesia	9.9%	Nu-DESC
Surgical ICU	Pandharipande[8]	Surgical ICU	73%	CAM-ICU
		Trauma ICU	67%	
Head and neck	Weed[9]	Major head and neck	17%	Not stated
Cardiac	Kazmierski[10]	Cardiac surgery with CPB	Age <60: 16.3% Age ≥60: 24.7%	DSM-IV
	Rudolph[11]	Patients >60 undergoing elective or urgent cardiac surgery	43%	CAM
	Saczynski[12]	Patients >60 undergoing elective coronary artery bypass grafting or valve replacement surgery	46%	CAM
Vascular	Marcantonio,[13] Schneider,[14] Bohner,[15] and Benoit[16]	Abdominal aortic aneurysm repair	33-54%	CAM or DSM-IV

	Schneider,[14] and Bohner[15]	Peripheral vascular	30-48%	DSM-IV
Orthopedic	Fisher[17]	Patients >60 undergoing elective orthopedic procedures	17.5%	CAM
	Marcantonio[18] and Lee[19]	Patients >65 undergoing emergent hip fracture repair	30.2-41%	CAM

Table 1: Incidence of Delirium in Major Surgeries. CAM, Confusion Assessment Method; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ICU, Intensive Care Unit; Nu-DESC, The Nursing Delirium Screening Scale

The diagnostic criteria for delirium have recently been updated in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Delirium is an acute neurocognitive disorder characterized by a fluctuating level of consciousness with impairment of attention and cognition. In the postoperative context, delirium typically manifests between 0 and 96 hours following the surgical intervention. It is unclear why postoperative delirium occurs so frequently. Age greater than 60, male gender, history of dementia or depression, sensory impairment, and chronic medical illness are consistently described as risk factors for delirium.[20] No effective prophylactic or curative treatments for postoperative delirium have been identified.

Ketamine and Delirium

Ketamine is an anesthetic agent that has been in common use for more than 50 years. Ketamine has a wide margin of safety, and as of 2005 had been studied in over 12,000 operative and diagnostic procedures, involving over 10,000 patients from 105 separate studies (Ketamine package insert 2005). There is a pharmacological rationale for using ketamine as a preventative measure against postoperative delirium based on its N-methyl-D-aspartate (NMDA) antagonism.[21] Normally, excitatory amino acids such as glutamate and aspartate act as agonists at NMDA receptors, and, in the setting of surgery and inflammation, they might

promote excitotoxic injury and apoptosis.[21] As an NMDA antagonist, ketamine has the potential to protect against such neurological injury.[22] Ketamine has also been posited to inhibit HCN1 receptors, which mediate the hyperpolarization-activated cation current.[23] Such inhibition is pertinent to delirium because HCN1 channels are important for regulating states of consciousness[24] and are up-regulated by inflammation.[25] HCN1 receptors are also thought to play a critical role in neuropathic pain through inflammatory cascades.[26]

Based on the pharmacological rationale for neuroprotection, a 58-patient randomized, controlled trial was conducted to determine whether ketamine might prevent delirium after major cardiac surgery.[27] There was a significant reduction in postoperative delirium from 31% to 3% with the administration of low dose ketamine (0.5 mg/kg) upon induction of anesthesia. While encouraging, this trial must be regarded as preliminary owing to its small sample size, and single center design. Interestingly, the same investigators also found that ketamine was associated with improved cognition beyond the immediate postoperative period.[28] Differences between the ketamine and placebo groups were evident in tests of nonverbal memory, verbal memory, and executive function. The investigators found that C reactive protein, a non-specific inflammatory marker, was similar at baseline in the ketamine and the placebo groups. On the first postoperative day, C reactive protein was elevated in both groups, but was significantly higher in the placebo group. The investigators hypothesized that the neuroprotective effect of ketamine might have been, in part, attributable to its anti-inflammatory actions.[28] In support of the plausibility of this hypothesis, ketamine use in another cardiac surgical population was similarly shown to attenuate postoperative increases in inflammatory markers.[29]

Intraoperative sub-anesthetic dose ketamine is appealing as a potential preventative intervention for delirium, since it is inexpensive and has an excellent safety profile. A number of questions remain to be answered regarding postoperative delirium. Despite the fact that delirium is a common and serious postoperative complication, intraoperative factors contributing to pathogenesis have not been rigorously investigated, and only a few small trials have been

conducted examining interventions to decrease its incidence. It is also currently unknown whether postoperative delirium is preventable, particularly in patients with underlying vulnerabilities. Importantly, ketamine in higher (anesthetic) doses has become less popular over time owing to side effects, including hallucinations and emergence reactions, especially in younger patients.[30,31] To ensure treatment effectiveness, the preliminary results identifying sub-anesthetic dose ketamine as a useful preventative intervention for postoperative delirium should therefore be confirmed or refuted using a large scale, pragmatic, randomized controlled trial design prior to routine adoption of low dose ketamine for this purpose.

Acute and Persistent Pain

Similar to delirium, both acute and persistent pain are common postoperative complications, with a negative impact on patients' lives. The Joint Commission has established the prevention of severe postoperative pain as a benchmark of quality,[32] and adequate pain management is increasingly viewed as a fundamental human right.[33,34] Unfortunately, this standard of care has not been attained to date; it has previously been estimated that about a third of patients suffer severe acute postsurgical pain following major procedures.[35] Furthermore, patients who have acute postoperative pain are more likely to develop chronic pain, and the incidence of persistent postoperative pain following major surgeries remains between 5% and 30%.[36] As an antagonist at NMDA and HCN1 receptors, ketamine has powerful analgesic properties. A systematic review showed that a single sub-anesthetic dose of intraoperative ketamine was associated with decreased visual analog pain scores up to 48 hours postoperatively.[37] At 24 hours postoperatively, ketamine was associated with an impressive 16 mg decrease in total morphine consumption.[37] Furthermore, adverse effects such as hallucinations were rarely reported when low dose ketamine was administered during general anesthesia.[37] Consistent with these findings, a Cochrane systematic review reported that sub-anesthetic doses of perioperative ketamine were associated with decreased postoperative pain, decreased morphine

consumption, and decreased nausea and vomiting.[38] Adverse effects were mild or absent.[38] An updated systematic review, which included 70 small studies involving 4,701 patients, recently confirmed that, in a dose-dependent manner, sub-anesthetic intraoperative ketamine was consistently associated with decreased postoperative pain despite decreased opioid consumption.[39] The more painful the surgical procedure, the greater was the analgesic benefit attributable to ketamine.[39] In keeping with decreased opioid consumption, postoperative nausea and vomiting were also less frequent in patients who received ketamine. However, patients who had been randomized to ketamine reported hallucinations and nightmares more frequently.[39] While efficacy data, based on numerous small studies, strongly suggest that supplementary ketamine should be used to decrease pain and opioid usage postoperatively, most practitioners have not incorporated low dose ketamine into their routine practice. Preliminary data gathered from 5 institutions (see below for details) involved in the PODCAST Trial suggest that, despite their knowledge regarding the analgesic and opioid-sparing effects, practitioners do not administer low-dose ketamine for pain because of concern for complications such as delirium. Thus, effectiveness data regarding the relationship of ketamine, delirium and pain are needed. Although numerous small efficacy studies have shown that ketamine decreases acute postoperative pain, its role in preventing persistent postoperative pain has not been rigorously explored. Many causal mechanisms that are thought to be implicated in persistent pain and a single intraoperative intervention might not be sufficient to decrease its occurrence. However, there have been encouraging findings about the potential of NMDA antagonists to decrease postoperative persistent pain. In the ENIGMA trial, patients were randomized to receive intraoperative oxygen with either nitrogen or nitrous oxide, which, like ketamine, is an NMDA antagonist. The investigators found that among those patients who received nitrous oxide, there was an absolute decrease in the percentage of patients who experience persistent pain (baseline incidence = 15%) at 3 months postoperatively of 7% (95% CI, 1.9% to 13.9%).[40] A randomized study has examined the potential beneficial effect of intraoperative ketamine on

persistent postoperative pain among patients undergoing total hip replacement.[41] This trial found a reduction in the ketamine group from 21% to 8% (reduction = 13%; 95% C.I., 1.3% to 24.9%) in patients experiencing persistent pain at 6 months after their surgery.[41] The PODCAST study would demonstrate whether sub-anesthetic dose intraoperative ketamine is effective at preventing acute postoperative pain in a real world setting. If ketamine were shown to have a substantial effect in decreasing acute postoperative pain, a next step would be to investigate rigorously its impact on persistent pain.

Current Utilization of Low-Dose Ketamine

A survey of anesthesia clinicians was conducted at five of the institutions (Washington University in St. Louis, University of Michigan, University of Manitoba, Weill Medical College of Cornell University, and Medical College of Wisconsin) participating in the PODCAST clinical trial. In total, 270 clinicians responded to the surveys; 18% (range among institutions 12% to 40%) of respondents currently incorporate adjunctive sub-anesthetic ketamine into their practice. Interestingly, 84% of survey respondents believe that low dose ketamine decreases acute postoperative pain, 81% feel that it decreases postoperative opioid consumption, and 51% believe that it decreases chronic postoperative pain. However, the reason that a minority of practitioners are currently administering adjunctive ketamine is probably because many remain concerned about the neurological side effects of even low dose ketamine; 68% of respondents expressed concern about hallucinations, 62% about delirium and 55% about nightmares.

Potential Impact of PODCAST

The PODCAST trial has a novel focus in that it is assessing the impact of an intervention (sub-anesthetic ketamine administration) on both delirium and pain, two adverse and potentially linked outcomes that have not previously been jointly evaluated in a single large clinical trial.

Both delirium and pain are surprisingly common acute postoperative complications with major negative consequences for patients.[1,35] Currently, there are no official guidelines to screen patients for delirium and only few preventive measures have been investigated, with disappointing results. Since most patients with postoperative delirium have a hypoactive phenotype, it is frequently missed in clinical practice. As noted previously, postoperative delirium is associated with increased intensive care and hospital stay, with persistent cognitive decline and with increased mortality. Thus, any intervention that could decrease the incidence of postoperative delirium would probably have major positive implications for older patients undergoing surgical procedures. Unlike delirium, acute postoperative pain is routinely assessed and the Joint Commission has prioritized the prevention of severe postoperative pain as a universal goal. Unfortunately this objective has not been met, and both severe acute pain and debilitating chronic pain continue to afflict many surgical patients.[35,36] Of note, both pain and its treatment with opioid analgesics can be risk factors for delirium. Opioid analgesics are the mainstay therapy for postoperative pain, but their administration is curtailed in older patients particularly for safety considerations regarding respiratory depression, but also for concerns about causing sedation and delirium.

Pragmatic trials are intended to generate evidence of effectiveness of a test, treatment, procedure, or health-care service.[42,43] At present, there is a lack of pragmatic trials for candidate interventions to prevent important and common postoperative neurologic and psychiatric complications including delirium and pain. Ketamine is a plausible prophylactic option for each of these neurological and psychiatric complications. The American Society of Anesthesiologists has published Practice Guidelines for the management of acute and chronic pain, which, based on small efficacy or observational trials, include ketamine as a treatment option.[44,45] There are currently no guidelines for the prevention of postoperative delirium. Thus, a multicenter pragmatic trial comparing low dose ketamine with placebo is timely. It is important to emphasize

that any one of several potential results of the PODCAST trial will have important and immediate positive implications for older surgical patients. First ketamine might decrease both delirium and pain. This result would provide clear support for a larger comparative effectiveness trial testing ketamine as a prophylactic measure for both of these outcomes. Second, ketamine might decrease pain without increasing delirium. This result would provide compelling data that encourage the use of ketamine to prevent pain without concern for cognitive side effects such as delirium. Third, ketamine might decrease delirium and have no impact on pain. Although the lack of effect on pain is unlikely, this result would also encourage further study of the use of prophylactic intraoperative ketamine. However, low dose ketamine may be found to increase delirium, regardless of its impact on pain. This result would suggest that the incorporation of intraoperative ketamine into routine clinical practice for older surgical patients is not warranted and would negate the need for a larger pragmatic trial. Furthermore, the PODCAST trial will help determine ketamine dose-related effects by comparing two doses (0.5 mg/kg and 1 mg/kg) to placebo. As such, all of these potential results of the PODCAST trial have the potential to impact clinical practice and will be generalizable to all older surgical patients undergoing major surgical procedures because of the permissive inclusion criteria and the simplicity of intervention.[42]

METHODS AND ANALYSIS

Study design

PODCAST is a prospective randomized controlled trial has been designed in accordance with CONSORT guidelines[46] and will evaluate whether a single bolus dose of ketamine (0.5 mg/kg or 1 mg/kg) following induction of anesthesia and before surgical incision decreases the incidence or severity of postoperative delirium and pain in a mixed elderly (>60 years) surgical patient population. Patients will undergo the standard preoperative anesthesia assessment. Follow up

information will be collected from the medical chart for up to 5 years. The overall study design is outlined in Figure 1.

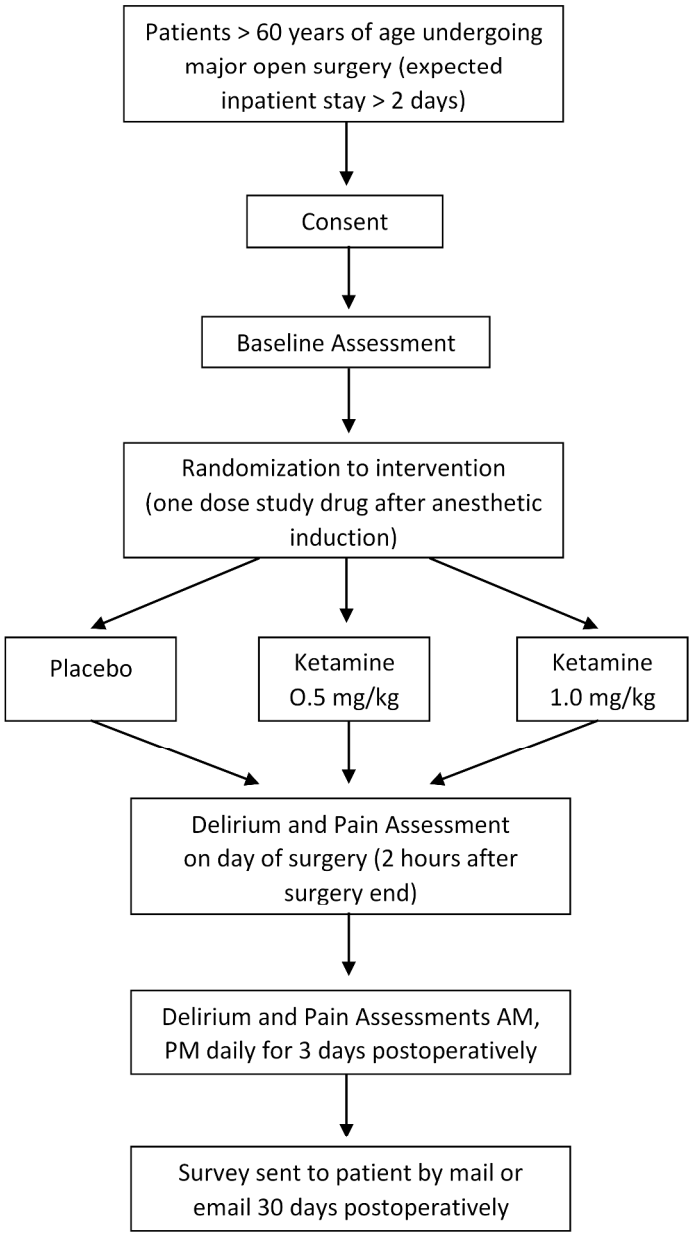

Figure 1: Study Enrollment

Eligibility criteria

Patients 60 years old and older, who are competent to provide informed consent and who are undergoing major open cardiac surgery (e.g., coronary artery bypass graft, valve replacement) or non-cardiac surgeries (e.g., thoracic surgery, major vascular surgery, intra-abdominal surgery, open gynecologic surgery, open urologic surgery, major orthopedic surgery, hepato-biliary surgery and major ENT surgery) receiving general anesthesia will be eligible for inclusion. The exclusion criteria are based on the contraindications to ketamine from the 2005 ketamine package insert. Patients with an allergy to ketamine and those in whom a significant elevation of blood pressure would constitute a serious hazard (e.g., pheochromocytoma, aortic dissection) will be excluded. We shall also exclude patients with drug misuse history (e.g., ketamine, cocaine, heroin, amphetamine, methamphetamine, MDMA, phencyclidine, lysergic acid, mescaline, psilocybin), patients taking anti-psychotic medications (e.g., chlorpromazine, clozapine, olanzapine, risperidone, haloperidol, quetiapine, paliperidone, amisulpride, sertindole), and patients with a weight outside the range 50 kg – 200 kg (110 lbs – 440 lbs). Patients will be enrolled either during a preoperative clinic visit or in the hospital prior to surgery.

Baseline Assessment

At the time of enrollment, patients will undergo the same delirium and pain evaluation that will be used postoperatively (see Outcomes section). Additionally patients will be screened for functional dependence using the Barthel Index of Activities of Daily Living,[47] for depression using the patient health questionnaire (PHQ-8),[48] and for obstructive sleep apnea using the STOP-Bang criteria.[49] Patients will be asked if they have a history of delirium, and if this presented after surgery. They will also be asked about any falls they have experienced in the six months prior to surgery. Comorbid conditions, including the components of the Charlson Comorbidity Index,[50] will be obtained by reviewing the patients' medical records. Any available preoperative lab results, including electrolytes and blood counts, will also be recorded.

Interventions

As this is a pragmatic trial, apart from administration of the study drug (ketamine or normal saline), all decisions about anesthetic technique will be made by the anesthetic team assigned to each patient. The only exception is that clinicians will be instructed not to administer any ketamine other than the study drug. The intention of this trial is to interfere as little as possible with the usual process of care, which will increase the applicability of the findings.[43] Following induction of general anesthesia, an intravenous dose of 0.5 mg/kg ketamine, 1 mg/kg ketamine, or an equivalent volume of normal saline will be injected via a reliable (free flowing) central or peripheral intravenous line. Clinicians will be blinded to the treatment arm of the study. Anesthetic factors such as the use of nitrous oxide, protocols for pain prevention, use of neuraxial anesthesia, use of nerve blocks, and other practices that could potentially affect primary or secondary outcomes will be assessed in a *post hoc* manner.

Outcomes

Primary outcomes

Trained members of the research team who are blinded to the treatment arm of the study will assess patients for **delirium** (primary outcome) using the Confusion Assessment Method (CAM)[51] and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[52,53] for patients who are unable to speak (e.g., have a tracheal tube or tracheostomy) on the intensive care unit. (Appendix A and B). These methods (the CAM and the CAM-ICU) have been shown to be reliable and to have good agreement with the DSM-IV criteria for delirium.[53-55] Delirium assessments will be performed when patients can be aroused sufficiently in order to be assessed for delirium (Richmond Agitation and Sedation Score > -4). The first delirium assessment will be attempted if feasible on the day of surgery in the afternoon / evening. Patients will then be assessed for delirium twice daily (from postoperative day 1 to postoperative

day 3) in the morning and in the afternoon / evening with at least 6 hours between assessments. Each patient will be assessed for delirium up to seven times. At the Washington University site, the patients' family members will perform the Family Confusion Assessment Method (FAM-CAM) separately from the investigators performing their assessments. (Appendix C) Investigators and family members will be blinded to each other's assessments. The FAM-CAM has demonstrated high sensitivity and specificity for detection of delirium and good agreement with the CAM[56], but has not been specifically evaluated in the postoperative setting. After the final delirium assessment, patients will complete the Delirium and Pain Self-Assessment Questionnaire (Appendix D). Incident delirium subsequent to this period is unlikely to be directly related to anesthetic or other intraoperative factors.

Secondary outcomes

Study team members blinded to the treatment group of the patient will assess all secondary outcomes. **Acute pain** (secondary outcome) will be assessed prior to surgery and then postoperatively by using the Behavioral Pain Scale (BPS)[57] or the Behavioral Pain Scale for the Non-Intubated patient (BPS-NI)[58] and the 10-cm VAS (Visual Analog Scale) (Appendix E and F) at the same times as patients are assessed for delirium. The BPS-NI has been shown to be a valid and reliable tool for measuring pain in a predominantly delirious patient population.[58] Interviewers will rate the BPS or BPS-NI prior to asking the patient to complete the VAS to prevent bias in the BPS and BPS-NI assessments. Postoperative daily amount of opioids and sedatives administered will be ascertained from the patient's electronic health record spanning the period after surgery until the final delirium assessment is complete. After the final delirium assessment, patients will complete the Delirium and Pain Self-Assessment Questionnaire (Appendix D). **Postoperative nausea and vomiting** (secondary outcome) will be assessed at the same time points that patients are assessed for delirium by asking patients to rate the

severity of their nausea and vomiting, if present, on a three point scale (mild, moderate, severe). Patients will be questioned at each assessment about side effects, especially hallucinations and nightmares. Intensive care unit and hospital length of stay will be obtained from the patient's medical record. At some of the participating sites in the PODCAST trial, patients will receive a survey, which will be sent by mail or email one month following surgery. This survey will collect patient reported outcomes (PROs) on depressive symptoms, affect, persistent pain, functionality and quality of life. Depressive symptoms will be assessed with the eight item Patient Health Questionnaire (PHQ-8), Affect will be assessed with two 10-item mood scales that comprise the Positive and Negative Affect Schedule (PANAS) within three to six months postoperatively.[59] The same screens for depressive symptoms and affect will also be conducted in the hospital on postoperative day 3. Persistent pain will be assessed with the Brief Pain Inventory Short Form (BPI-SF). The Barthel Index will be used to report functionality and quality of life will be assessed from the Veteran's Rand-12 (VR-12) questionnaire.

Standardization of training and outcomes assessment

All study team members who perform delirium assessments will undergo a rigorous training process. For the initial training, representatives from each study site participated in a full-day training program led by Dr. Sharon Inouye, the original creator of the CAM. Those who attended this initial training will oversee the training of other team members at their sites. Trainees must demonstrate competence at both conducting CAM interviews and in scoring these interviews. For the initial part of training, trainees must conduct at least two satisfactory CAM interviews in the presence of a trained team member. These interviews will not be on patients enrolled in the PODCAST trial. To establish their ability to score CAM interviews reliably, trainees will accompany trained team members to conduct CAM interviews. A trained member of the research team will conduct each CAM interview for patients enrolled in the

PODCAST trial. The trainee will observe the interview, but will score the CAM independently. The trainee must agree with the trainer on the presence or absence of all twelve cognitive features assessed by the CAM on a minimum of two delirious and two non-delirious patients. After meeting the stipulations of training, the newly trained team member will conduct their first interview of a patient enrolled into the PODCAST trial in the presence of a previously trained team member.

Assessment of the standardization and reliability of delirium assessments

After training, all PODCAST team members administering delirium assessments will be invited to participate in a project to demonstrate the validity and reliability of the CAM in our study population. Participants will view and rate eight videos of standard interviews depicting delirious and non-delirious patients. Participants will independently score the CAM for each scenario. Demographic information, level of education, level of clinical experience, and primary language will also be collected from all participants. Data will be de-identified. All scores and data will be submitted to the lead site, Washington University. The group's scores will then be compared to determine the reliability of delirium assessments across sites. Additionally, the group's scores will be compared to a set of "gold standard" scores for the videos (determined by Dr. Inouye's team) This comparison is intended to demonstrate validity of the CAM in our study setting. Overall, the goal of the project is to demonstrate standardization of the delirium outcome across all study sites.

Sample size

Based on published delirium incidences in the scientific literature (Table 1), we estimate conservatively that the incidence of postoperative delirium in a mixed major surgical population

of older patients will be between 20% and 25%. Based on data from a sub-study of the BAG-RECALL trial that we have recently completed, the incidence of delirium among patients admitted to our cardiothoracic intensive care unit at Barnes-Jewish Hospital is 25% within three postoperative days. Hudetz et al found that ketamine was associated with a 28% (95% CI, 8% to 46%) absolute risk reduction in delirium (from a baseline incidence of 31%).[27] A 28% reduction is likely to be an over-optimistic effect size for designing a pragmatic study; 10% is more realistic as the most optimistic effect size and remains consistent with the confidence interval for the effect size found by Hudetz et al.[27] Assuming a two-sided type I error rate of 5%, a sample size of 600 will give greater than 80% power to detect a decrease in the incidence of delirium from 25% to 15% with ketamine. On the other hand, we consider the minimum clinically important difference (MCID) or effect size to be 2%, which corresponds to a number needed to treat of 50 surgical patients to prevent one episode of delirium. The rationale for the low MCID is that delirium is a serious postoperative complication that is associated with increased mortality and the proposed intervention (low dose ketamine) is safe, inexpensive and not likely to have adverse effects.

There are two specific issues to clarify in this study: i) the likely effect size with ketamine; and ii) the optimal ketamine dose. Ketamine might increase delirium, decrease delirium or have no impact on delirium. If ketamine increases delirium, it is more likely to increase delirium at a higher dose (1 mg/kg). If ketamine decreases delirium, it might have a dose response effect – less delirium at the higher ketamine dose (1 mg/kg). We anticipate that ketamine will decrease pain in a dose dependent manner – 1mg/kg will be superior to 0.5 mg/kg. Accrual of 200 patients to each dose of ketamine along with a placebo arm will allow a more robust assessment of the dose-response efficacy for postoperative analgesia than previous studies with fewer numbers. In general, the higher ketamine dose might have more side effects. As such, this trial might inform whether the higher ketamine dose can be used, in view of its

possibly superior analgesia, with a potential benefit in relation to delirium and without excessive side effects. The dosage determination going forward will depend on the observed incidence of delirium with each dose, analgesia efficacy with each dose, and side effect profile with each dose. The proposed design for the study is shown in Table 2.

Group	**N**
Placebo	200 patients
Ketamine Low Dose (0.5 mg/kg)	200 patients
Ketamine Moderate Dose (1 mg/kg)	200 patients

Table 2: Patient Allocation.

With this approach, we believe that this study will clearly inform whether it is indicated, both in terms of efficacy and in terms of feasibility, to pursue a larger study. The purpose of the larger study (PODCAST2) will be to determine definitively whether ketamine is associated with a reduction in delirium (and pain) in high-risk older surgical patients, without incurring an increase in side effects. As the main effect evaluated will be whether ketamine decreases delirium, Table 3 provides a useful guide for the potential findings of the current study with their implications.

Delirium Incidence in Placebo Groups (N=200)	**Delirium Incidence in Ketamine Groups (N=400)**	**Effect Size (Reduction in delirium with ketamine)**	**95% Confidence Interval (CI) for Effect Size**
25% (N=50)	25% (N=100)	0%	-7.6% to 7.1%
Implication: Consider Pursuing a larger study only if pain is decreased in ketamine groups, and there is no increase in side effects.			
25% (N=50)	22.5% (N=90)	2.5%	-4.5% to 10.0%
Implication: Although the point estimate is >2% (MCID), a 9,500 patient study would be required to			

clarify more precisely the effectiveness of ketamine in preventing delirium. Other outcomes in the study (e.g., pain reduction and side effects) would inform the approach.			
25% (N=50)	20% (N=80)	5%	-1.9% to 12.4%
Implication: Pursue larger study with approximately 2,500 patients to clarify more precisely the effect of ketamine on preventing delirium.			
25% (N=50)	17.5% (N=70)	7.5%	0.7% to 14.8%
Implication: Pursue larger study (approximately 1,200 patients) to clarify whether effect size >2% (MCID) and to define it more precisely.			
25%	15%	10%	3.3% to 17.1%
Implication: For main effect, lower bound of CI >2% (MCID). Ketamine's benefit in decreasing delirium is very likely, but a larger study (approximately 1,200 patients) would define its effect more precisely.			

Table 3: Potential Findings of PODCAST.

Recruitment

This clinical trial will be conducted at Washington University in St. Louis and other sites. Our research team has conducted large randomized, controlled trials, which enrolled (approximately) 2,000 patients over 14 months in the B-unaware trial,[60] 6,000 patients over 26 months in the BAG-RECALL trial[59] and 22,000 patients over 24 months in the Michigan Awareness Control Study.[61] Based on the inclusion criteria and the number of eligible surgical patients, we estimate that one year will be sufficient for patient enrollment to the proposed trial, and a further one year for data analysis.

Allocation

Subjects will be block randomized by the hospital pharmacy departments in groups of 15 (1:1:1 ratio - 0.5 mg/kg ketamine: 1 mg/kg ketamine: placebo), stratified by site, in order to keep the randomization balanced and the groups more homogeneous. The outcome of this random

assignment will be concealed from the study team and all study subjects and trial staff will be blinded to the randomization. Codes will be held by the hospital pharmacies and they will dispense medication. Randomization codes will remain concealed until the primary analysis is completed. Prepared syringes of either placebo or ketamine will be directly delivered to the operating room in which surgery of the consented patient will take place as soon as the research team informs the pharmacy about the patient going to the operating room for surgery.

Data analysis and management

Data analysis for this investigation will require comparisons of patient outcomes (e.g., delirium, pain, length of stay, adverse events) in the three study groups to assess for significant differences among ketamine doses (placebo, 0.5 mg/kg and 1 mg/kg). For proportions and categorical outcomes, such as incident delirium, we will use the chi square test (or Fisher's exact test in the case of sparse data) to compare proportions across the three groups and the Cochran-Armitage test to test for dose response trends. For continuous outcomes, such as visual analog pain scores and opioid consumption, we will use repeated–measures analysis of variance tests to detect the main effects. The Tukey post-hoc test will also be run on all significant interactions to determine differences between individual and combined groups (e.g., placebo versus combined ketamine groups; 0.5 mg/kg ketamine versus 1 mg/kg ketamine). For multivariate analyses, we will apply the Cox proportional-hazards model for recurrent events to investigate the effects of low doses of intraoperative ketamine on delirium by comparing its occurrence and timing across the study groups. We will also model the number of postoperative delirium incidents using a Poisson hurdle regression to find out the difference in the proportion of patients with and without delirium, and for those who experience delirium, the difference in its recurrence. Both models (Cox proportional-hazards and hurdle model) will account for differences in ketamine effectiveness in cardiac versus non-cardiac surgery by including

interaction terms for ketamine dose and cardiac surgery status, while adjusting for other influential variables. We will also use mixed-effects regression models to assess differences among the subgroups in continuous outcome variables over time (e.g., postoperative pain scores and opioid consumption). These models will likewise account for interactions between ketamine dose and cardiac surgery status. All statistical testing will be two sided, and p values <0.05 will be regarded as significant. No interim analyses are planned. Appropriate adjustment will be made for multiple analyses.

The Division of Biostatistics Informatics Core at Washington University will be used as a central location for data processing and management. Washington University belongs to a consortium of institutional partners that work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Division of Biostatistics Informatics Core. The iterative development and testing process result in a well-planned data collection strategy for individual studies. REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics at Washington University. All web-based information transmission is encrypted. The data is all stored on a private, firewall protected network. All users are given individual user ids and passwords and their access is restricted on a role-specific basis. REDCap was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Washington University guidelines. REDCap currently supports >500 academic/non-profit consortium partners on six continents and 38,800 research end-users.[62]

Monitoring

The research team will monitor the study for adverse events. All serious adverse events will be reported to the IRB according to IRB stipulations. The monitoring plan for this study is appropriate for the planned pragmatic trial. As an anesthetic drug, ketamine has an excellent safety profile and record. In particular, low dose ketamine (0.5 mg/kg or 1 mg/kg) administered prior to surgical incision is unlikely to be associated with major adverse events, and even minor side effects manifesting after induction of anesthesia and the start of surgery are improbable.[37,38,63]

The PODCAST trial will have an appropriate data and safety monitoring plan for a low risk clinical trial. There will be a charter to guide the functions of the Data Safety and Monitoring Board (DSMB), and the DSMB will produce reports in accordance with NIH guidelines. The DSMB will provide independent oversight of the PODCAST trial and will review general conduct of the trial as well as study data for participant safety.[64] The DSMB will be comprised of independent, multidisciplinary experts who will make recommendations regarding the continuation, modification, or termination of the trial.[65] The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments to which the patients have consented to participate, and to assure the regulatory bodies and the public (and possibly funding agencies) that conflicts of interest do not compromise either patient safety or trial integrity.[66] There will be no pre-specified interim analysis given the size of this study; frequent analyses might increase the likelihood of bias.[64] There will be a provision for early stoppage for safety concerns, but not for efficacy or for futility.[64] Trials that stop early for benefit show implausibly large treatment effects, particularly when the number of events is small.[67] Truncated trials have been associated with greater effect sizes than trials not stopped early, independent of the presence of statistical stopping rules.[68]

All members of the DSMB will be at the Washington University site. Local investigators at all participating sites will report serious adverse events, or unanticipated problems involving risks to subjects or others, to their IRB and to the PI of the study at Washington University. If such problems are considered related to the trial, then they will also be reported to IRBs at other participating sites and to the chairperson of the DSMB. The members of the DSMB will have no direct involvement in the conduct of the PODCAST trial. Neither will they have financial, proprietary or professional conflicts of interest, which may affect the impartial, independent decision-making responsibilities of the DSMB.[64,65] Letters of invitation to prospective DSMB members will include the following: "Acceptance of this invitation to serve on the PODCAST DSMB confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." All DSMB members will sign a Conflict of Interest Certification to confirm no conflict exists. There will be between three and eight people on the DSMB, in order to optimize performance.[69] The DSMB will be advisory rather than executive on the basis that it is the PODCAST trial investigators who are ultimately responsible for the conduct of the trial.[69]

The risks associated with this study are low. There is a rare risk of breach of confidentiality. In contrast to other anesthetics, protective reflexes such as coughing and swallowing are maintained with low dose ketamine. The 2005 package insert for ketamine reports the induction dose for anesthesia as follows: The initial dose of ketamine administered intravenously may range from 1 mg/kg to 4.5 mg/kg. The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg. The short-term side effects of ketamine at higher doses (>1-2 mg/kg) than the dosages proposed for this study (0.5 mg/kg or 1 mg/kg) include tachycardia, nystagmus, hypersalivation, euphoria, emergence reactions, hallucinations and nightmares.[70] It is possible, but very unlikely, that low dose ketamine (0.5 mg/kg or 1 mg/kg) administered just after induction of anesthesia or administration of sedative medications will

cause these side effects.[37,38,63] Emergence reactions, hallucinations and nightmares are more common in younger patients receiving ketamine. In published studies on low dose ketamine (0.25 to 1 mg/kg) administered during general anesthesia, side effects have generally not been found.[37] The main side effects that might occur are nightmares and hallucinations. Other neuropsychiatric side effects might occur, most likely within the first 24 hours after surgery, and will be determined from patient interviews. The incidence of these side effects in this patient population is currently unknown, and thus side effects will be reported separately and jointly. Meta-analysis suggests that ketamine might be associated with an increase in neurologic and psychiatric side effects from approximately 5% to 7.5%. This study will be >80% powered to detect an increase in side effects from 5% to 12% and 20% powered to detect an increase in side effects from approximately 5% to 7.5%. As part of the informed consent process for this study, patients will be informed of the rare risks and will be asked about them after their surgery. In the unlikely event that serious side effects occur, they will be documented and will be reported to the human research protection office and to the study's DSMB. Participants will not incur any study-related expenses, nor will they be financially compensated for their participation.

Ethics and dissemination

Ethics approval and consent

The PODCAST trial has been approved by the institutional review boards of the principal investigators' home institutions (Washington University, St. Louis and University of Michigan, Ann Arbor). Institutional review board approval has also been obtained at some of the participating sites (Postgraduate Institute of Medical Education and Research, Chandigarh, India; University of Manitoba, Winnipeg, Canada; Weill Medical College, Cornell University, New York City; Medical College of Wisconsin, Milwaukee) and is ongoing at other sites. Recruitment is anticipated to began in February of 2014 and continue through 2015. Potential participants

will be approached for enrollment by a member of the research team who will explain the purpose of the study and written informed consent will be obtained for all participants. Patients may choose not to participate in this study and there will be no penalty in terms of the care that they receive.

Confidentiality

Necessary protected health information will only be shared with members of the research team. To help protect confidentiality, research charts will be stored in a locked cabinet inside the locked research office. Electronic data and demographic information will also be kept in a password-protected electronic database stored on the departmental network drive and only accessible via password-protected departmental computers. A member of the research team will enter this information. Code numbers, rather than names, will appear on any data and documents used for evaluation or statistical analyses.

Dissemination

Dissemination plans include presentations at local, national and international scientific conferences. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript.

CONCLUSIONS

In the next four decades, the US population over the age of 60 is predicted to double to more than 80 million individuals. The aging population often requires surgery, which can be frequently complicated by postoperative pain and delirium. Delirium is defined as an acute brain dysfunction that presents as fluctuating levels of inattention and disordered thinking, and has been reported to affect up to 70% of surgical patients older than 60. Likewise, severe

postoperative pain continues to affect a large proportion of surgical patients, especially the elderly, and is another major contributor to delirium. Unfortunately, opioid medications, the current standard for analgesia, can themselves lead to delirium and other adverse consequences. Clinicians therefore face the paradox that both pain and the mainstay treatment of pain can lead to delirium. Although causal relationships have not been established, postoperative delirium is associated with increased intensive care unit and hospital stay, persistent cognitive decline, and increased mortality rate. What is needed is a therapeutic intervention that can both attenuate pain and decrease the occurrence of delirium. Mounting evidence suggests that the intraoperative administration of low dose (i.e., sub-anesthetic) ketamine, an anesthetic drug that has been in common use for 50 years, prevents delirium, lessens the severity of postoperative pain, and has an opioid-sparing effect. These multiple beneficial effects have been attributed to ketamine's anti-inflammatory and anti-excitotoxic actions. Despite these benefits, low-dose intraoperative ketamine currently does not enjoy widespread adoption, primarily because clinicians are concerned that the psychoactive properties of ketamine might compromise postoperative cognition. The PODCAST randomized controlled trial intends to address a gap in the field through an international, multicenter study that tests the effectiveness of ketamine in reducing both delirium and pain in surgical patients older than 60.

AUTHORS' CONTRIBUTORSHIP

Michael Avidan and George Mashour are the primary authors of the PODCAST protocol. Their contributions include drafting and editing the protocol, conceptualizing the study design, and organizing conduct across all sites. Bradley Fritz contributed to the PODCAST trial by editing the protocol, conceptualizing study design, creating the electronic database, REDCap used for data collection, and co-authoring a manual of operations for study conduct. Hannah Maybrier contributed to PODCAST by editing the protocol, co-authoring the manual of operations, recruiting patients for enrollment, collecting data, and coordinating the study across all sites. Maxwell Muench contributed to PODCAST by co-authoring a manual of operations, recruiting patients for enrollment, and collecting data. Krisztina Escallier contributed to PODCAST by editing the protocol, conceptualizing study design, and co-authoring a manual of operations. Yulong Chen contributed to PODCAST by editing the protocol and conceptualizing study design. Arbi Ben Abdallah contributed to PODCAST by editing the protocol and conceptualizing study design, including the statistical modelling of the study. Sharon Inouye contributed PODCAST by training investigators to perform delirium assessments and conceptualizing study design. Stephen Choi, Robert Downey, Hilary Grocott, Gyujeong Noh, Judith Hudetz, Eric Jacobsohn, Heiko Kaiser, Paul Pagel, Kane Pryor, Ryan Pong, Robert Veselis, and Virendra Kumar Arya contributed to PODCAST by editing the study protocol, conceptualizing study design, recruiting participants, and collecting data.

All authors including Avidan, Mashour, Fritz, Maybrier, Muench, Escallier, Chen, Ben Abdallah, Inouye, Veselis, Grocott, Hudetz, Pryor, Pagel, Arya, Pong, Jacobsohn, Gyujeong, Kaiser, Downey, and Choi have critically revised the PODCAST protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the PODCAST trial.

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COMPETING INTERESTS

None of the authors have conflicts of interest to disclose.

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Appendix A – Confusion Assessment Method

CONFUSION ASSESSMENT METHOD (CAM) SHORTENED VERSION WORKSHEET

EVALUATOR: DATE:

I. ACUTE ONSET AND FLUCTUATING COURSE

a) Is there evidence of an acute change in mental status from the patient's baseline? No ____ Yes ____

b) Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity? No ____ Yes ____

II. INATTENTION

Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said? No ____ Yes ____

BOX 1

III. DISORGANIZED THINKING

Was the patient 's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject? No ____ Yes ____

IV. ALTERED LEVEL OF CONSCIOUSNESS

Overall, how would you rate the patient's level of consciousness?

-- Alert (normal)

-- Vigilant (hyperalert)
-- Lethargic (drowsy, easily aroused)
-- Stupor (difficult to arouse)
-- Coma (unarousable)

Do any checks appear in this box? No ____ Yes ____

BOX 2

If all items in Box 1 are checked and at least one item in Box 2 is checked a diagnosis of delirium is suggested.

Adapted from Inouye SK et al, Clarifying Confusion: The Confusion Assessment Method. A New Method for Detection of Delirium. Ann Intern Med. 1990; 113:941-8.

Appendix B – Confusion Assessment Method for the Intensive Care Unit

CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the pt different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** **Command** Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If pt is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Overall CAM-ICU		
Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive	**Criteria Met →**	☐ **CAM-ICU Positive** (Delirium Present)
	Criteria Not Met →	☐ **CAM-ICU Negative** (No Delirium)

Appendix C – Family Confusion Assessment Method

Scoring the FAM-CAM

It is important to remember that the FAM-CAM is intended only to assist with screening and is not intended to provide a clinical diagnosis. If a positive score is suggested on the FAM-CAM, further evaluation with cognitive testing of the patient is necessary.

The FAM-CAM is considered positive if the following features are present: a) acute onset or fluctuating course **and** b) inattention **and** c) either disorganized thinking or altered consciousness. Several of the questions may help to identify whether these features are present, as outlined below.

Feature	Question #	Positive Answer
Acute Onset	Question 1,10	Yes, <4 weeks ago
-OR-		
Fluctuation	Question 9	"Come and go"
-AND-		
Inattention	Question 2	Yes
-AND EITHER-		
Disorganized Thinking	Question 3,5,6 (7 supportive)	Yes
-OR-		
Altered Consciousness	Question 4	Yes

Scoring Algorithm: Check the box if the respondent's answer is as indicated.
Delirium is suggested if there is **at least one check in each of the 3 columns.**

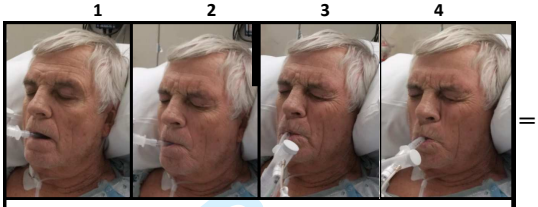
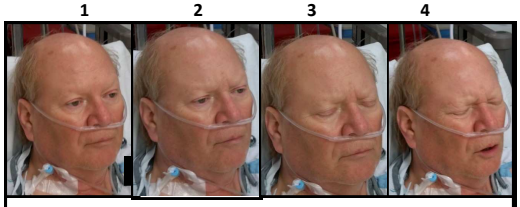
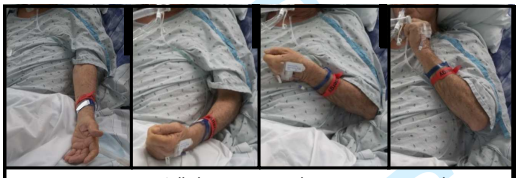
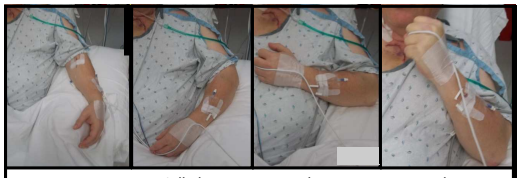
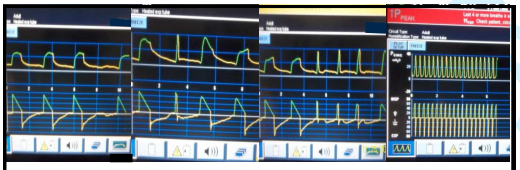
Question	Column 1 Acute Onset or Fluctuation	Column 2 Inattention	Column 3 Disorganized Thinking or Altered Level of Consciousness
Question 1 = yes? (Any Change)	☐		
Question 2 = yes? (Inattention)		☐	
Question 3 = yes? (Disorganized Speech)			☐
Question 4 = yes? (Excess Drowsiness)			☐
Question 5 = yes? (Disorientation)			☐
Question 6 = yes? (Perceptual Disturbance)			☐
Question 9 = "come and go"? (Fluctuation)	☐		
Question 10 = <4 weeks? (Acute Onset)	☐		

Delirium is suggested if there is **at least one check in each of the 3 columns.**
Delirium Suggested? _____ yes _____ no

Appendix E - Behavioral Pain Scale and Behavioral Pain Scale for the Non-Intubated Patient

Behavioral Pain Scale (BPS and BPS-NI) Scoring System

1 + 2 + 3 = Total BPS Value; from 3(no) - 12(max) pain behavior rated

	BPS (Intubated / Non-verbal)					BPS-NI (Non-intubated and verbal)				
	1	2	3	4		1	2	3	4	
1	 Relaxed	Partially tightened = brow lowering	Fully tightened = eyelids closed	Grimacing = folded cheek	=	 Relaxed	Partially tightened = brow lowering	Fully tightened = eyelids closed	Grimacing = folded cheek	
2	 No movement (At rest: mobilize limb to check tone)	Partially bent	Very bent; finger flexion	Retracted; opposition to care	=	 No movement (At rest: mobilize limb to check tone)	Partially bent	Very bent; finger flexion	Retracted; opposition to care	
3	 Tolerating ventilation	Coughing, but mostly tolerating ventilation	Fighting, but ventilation possible	Unable to control ventilation	≠	No pain vocalization	Moaning not frequent (≤3/min) and not prolonged (≤3s)	Moaning frequent (>3/min) or prolonged (>3s)	Howling or verbal complaint "Ow!," "Ouch!," or breath-holding	

Appendix D - Delirium and Pain Self-Assessment Questionnaire:

(Following the final delirium assessment, the following questionnaire will be given to patients):

A. Following your surgery, were there any periods that you felt you could not pay attention to people or things?

Yes No

B. If yes, can you say when:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

C. Following your surgery, were there any period that you felt you were not thinking in a logical or organized way?

D. If yes, can you say when:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

E. Did these feelings negatively affect your experience after the surgery?

Yes No

F. Following your surgery, were there any periods when your pain was uncontrolled?

Yes No

G. If yes, can you say when:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

H. Did any family members tell you that there were periods following your surgery that you felt you could not pay attention to people or things?

Yes No

I. Did any of your family members tell you that there were periods following your surgery when you were not thinking in a logical or organized way?

Yes No

J. Following your surgery, did you have bad dreams nightmares?

Yes No

K. If yes, can you say when:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

L. Following your surgery, did you have hallucinations (you saw things or heard things or felt things that were not there)?

Yes No

M. If yes, can you say when:

Today:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

For questions 1 to 3, the patient should use a pen to mark the VAS scale. The patient should be shown their previous responses to use as a reference.

1. What is your pain at **rest?**

no pain _____ worst pain imaginable

2. What is your pain when taking a **deep breath** (or coughing)?

no pain _____ worst pain imaginable

3. What is your pain when **moving** (sitting up, walking, or moving extremities)?

no pain _____ worst pain imaginable

4. If you have pain at rest or with movement, please indicate **where** (check all that apply)

Head/neck

Chest

Abdomen

Upper back

Lower back

Arms

Legs

5. Do you currently have **nausea and/or vomiting**?

None Mild Moderate Severe

6. Are you currently experiencing **anxiety?**

None Mild Moderate Severe

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1-3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	14
	6b	Explanation for choice of comparators	21
Objectives	7	Specific objectives or hypotheses	19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	21

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	30, 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	23
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	24
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	33
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	24
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	24-26
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	22

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	28
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	30
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	31
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	31
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	31
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	24-25
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	31
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	24-26
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	32
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	31
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	32
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	34
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	33
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	33
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	34
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	35
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	36
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	36
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	44
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	32
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	35
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	36
	31b	Authorship eligibility guidelines and any intended use of professional writers	36
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	36
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	separate file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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

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The Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) Study: Protocol for an International Multicenter Randomized Controlled Trial

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ABSTRACT

Introduction: Postoperative delirium is one of the most common complications of major surgery, affecting 10-70% of surgical patients 60 years and older. Delirium is an acute change in cognition that manifests as poor attention and illogical thinking, and is associated with longer ICU and hospital stay, long-lasting cognitive deterioration, and increased mortality. Ketamine has been used as an anesthetic drug for over 50 years and has an established safety record. Recent research suggests that, in addition to preventing acute postoperative pain, a sub-anesthetic dose of intraoperative ketamine could decrease the incidence of postoperative delirium as well as other neurologic and psychiatric outcomes. However, these proposed benefits of ketamine have not been tested in a large clinical trial.

Methods: The PODCAST study is an international, multicenter, randomized controlled trial. Six hundred cardiac and major non-cardiac surgery patients will be randomized to receive ketamine (0.5 mg/kg or 1 mg/kg) or placebo following anesthetic induction and prior to surgical incision. For the primary outcome, blinded observers will assess delirium on the day of surgery (postoperative day 0) and twice daily from postoperative days 1 to 3 using the Confusion Assessment Method or the Confusion Assessment Method for the ICU. For the secondary outcomes, blinded observers will estimate pain using the Behavioral Pain Scale or the Behavioral Pain Scale for Non-Intubated Patients and patient self-report.

Ethics and dissemination: The PODCAST trial has been approved by the ethics boards of five participating institutions; approval is ongoing at other sites. Recruitment began in February 2014 and will continue through 2016. Dissemination plans include

presentations at scientific conferences, scientific publications, stakeholder engagement and popular media.

Registration details: The study is registered at clinicaltrials.gov, NCT01690988 (last updated December, 2013).

The PODCAST trial is being conducted under the auspices of the Neurological Outcomes Network for Surgery (NEURONS).

STRENGTHS:

- The effects of ketamine are being observed in the routine clinical setting.
- Because PODCAST is a multicenter international trial, the results of the study will potentially be generalizable.
- This trial has a novel focus of assessing delirium and pain concurrently. Results could reveal that these two outcomes are potentially linked in the postoperative setting.
- PODCAST is a randomized, controlled double-blinded study.
- Investigators assessing for delirium have been appropriately trained and will use reliable and validated assessment tools.

LIMITATIONS:

- Pain is a subjective experience and is therefore difficult to measure.
- The Visual Analog Scale (VAS) is not a validated pain assessment instrument in delirious patients. In an attempt to mitigate this limitation, pain will also be assessed

observationally using the Behavioral Pain Scale (BPS) and the Behavioral Pain Scale – Non-intubated (BPS-NI).

- Delirium is fluctuating in nature. Because patients will be assessed at discrete time points, it is possible that some episodes of delirium will not be detected.

INTRODUCTION

Background and rationale

Delirium

Postoperative delirium is one of the most common complications of major surgery and affects between 10% and 70% of all surgical patients older than 60 years (Table 1).[1] The estimated additional healthcare costs associated with delirium exceed $60,000 per patient per year.[2] While causal relationships have not been established, delirium is associated with increased morbidity and mortality, prolonged length of hospital and intensive care unit (ICU) stay, functional and cognitive decline with nursing home or long-term care facility placement.[3-6] Furthermore, the acute deterioration in cognition and psychomotor agitation frequently seen with delirium is often distressing for both patients and their families.

Surgery type	Study (year)	Population	Delirium Rate	Detection method
Unselected	Radtke[7]	Recovery room after elective general anesthesia	9.9%	Nu-DESC
Surgical ICU	Pandharipande[8]	Surgical ICU	73%	CAM-ICU
		Trauma ICU	67%	
Head and neck	Weed[9]	Major head and neck	17%	Not stated
Cardiac	Kazmierski[10]	Cardiac surgery with CPB	Age <60: 16.3% Age ≥60: 24.7%	DSM-IV
	Rudolph[11]	Patients >60 undergoing elective or urgent cardiac surgery	43%	CAM
	Saczynski[12]	Patients >60 undergoing elective coronary artery bypass grafting or valve replacement surgery	46%	CAM
Vascular	Marcantonio,[13] Schneider,[14] Bohner,[15] and Benoit[16]	Abdominal aortic aneurysm repair	33-54%	CAM or DSM-IV

	Schneider,[14] and Bohner[15]	Peripheral vascular	30-48%	DSM-IV
Orthopedic	Fisher[17]	Patients >60 undergoing elective orthopedic procedures	17.5%	CAM
	Marcantonio[18] and Lee[19]	Patients >65 undergoing emergent hip fracture repair	30.2-41%	CAM

Table 1: Incidence of Delirium in Major Surgeries. CAM, Confusion Assessment Method; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ICU, Intensive Care Unit; Nu-DESC, The Nursing Delirium Screening Scale

The diagnostic criteria for delirium have recently been updated in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Delirium is an acute neurocognitive disorder characterized by a fluctuating level of consciousness with impairment of attention and cognition. In the postoperative context, delirium typically manifests between 0 and 96 hours following the surgical intervention. It is unclear why postoperative delirium occurs so frequently. Age greater than 60, male gender, history of dementia or depression, sensory impairment, and chronic medical illness are consistently described as risk factors for delirium.[20] No effective prophylactic or curative treatments for postoperative delirium have been identified.

Ketamine and Delirium

Ketamine is an anesthetic agent that has been in common use for more than 50 years. Ketamine has a wide margin of safety, and as of 2005 had been studied in over 12,000 operative and diagnostic procedures, involving over 10,000 patients from 105 separate studies (Ketamine package insert 2005). There is a pharmacological rationale for using ketamine as a preventative measure against postoperative delirium based on its N-methyl-D-aspartate (NMDA) antagonism.[21] Normally, excitatory amino acids such as glutamate and aspartate act as agonists at NMDA receptors, and, in the setting of surgery and inflammation, they might

promote excitotoxic injury and apoptosis.[21] As an NMDA antagonist, ketamine has the potential to protect against such neurological injury.[22] Ketamine has also been posited to inhibit HCN1 receptors, which mediate the hyperpolarization-activated cation current.[23] Such inhibition is pertinent to delirium because HCN1 channels are important for regulating states of consciousness[24] and are up-regulated by inflammation.[25] HCN1 receptors are also thought to play a critical role in neuropathic pain through inflammatory cascades.[26]

Based on the pharmacological rationale for neuroprotection, a 58-patient randomized, controlled trial was conducted to determine whether ketamine might prevent delirium after major cardiac surgery.[27] There was a significant reduction in postoperative delirium from 31% to 3% with the administration of low dose ketamine (0.5 mg/kg) upon induction of anesthesia. While encouraging, this trial must be regarded as preliminary owing to its small sample size, and single center design. Interestingly, the same investigators also found that ketamine was associated with improved cognition beyond the immediate postoperative period.[28] Differences between the ketamine and placebo groups were evident in tests of nonverbal memory, verbal memory, and executive function. The investigators found that C reactive protein, a non-specific inflammatory marker, was similar at baseline in the ketamine and the placebo groups. On the first postoperative day, C reactive protein was elevated in both groups, but was significantly higher in the placebo group. The investigators hypothesized that the neuroprotective effect of ketamine might have been, in part, attributable to its anti-inflammatory actions.[28] In support of the plausibility of this hypothesis, ketamine use in another cardiac surgical population was similarly shown to attenuate postoperative increases in inflammatory markers.[29]

Intraoperative sub-anesthetic dose ketamine is appealing as a potential preventative intervention for delirium, since it is inexpensive and has an excellent safety profile. A number of questions remain to be answered regarding postoperative delirium. Despite the fact that delirium is a common and serious postoperative complication, intraoperative factors contributing to pathogenesis have not been rigorously investigated, and only a few small trials have been

conducted examining interventions to decrease its incidence. It is also currently unknown whether postoperative delirium is preventable, particularly in patients with underlying vulnerabilities. Importantly, ketamine in higher (anesthetic) doses has become less popular over time owing to side effects, including hallucinations and emergence reactions, especially in younger patients.[30,31] To ensure treatment effectiveness, the preliminary results identifying sub-anesthetic dose ketamine as a useful preventative intervention for postoperative delirium should therefore be confirmed or refuted using a large scale, pragmatic, randomized controlled trial design prior to routine adoption of low dose ketamine for this purpose.

Acute and Persistent Pain

Similar to delirium, both acute and persistent pain are common postoperative complications, with a negative impact on patients' lives. The Joint Commission has established the prevention of severe postoperative pain as a benchmark of quality,[32] and adequate pain management is increasingly viewed as a fundamental human right.[33,34] Unfortunately, this standard of care has not been attained to date; it has previously been estimated that about a third of patients suffer severe acute postsurgical pain following major procedures.[35] Furthermore, patients who have acute postoperative pain are more likely to develop chronic pain, and the incidence of persistent postoperative pain following major surgeries remains between 5% and 30%.[36] As an antagonist at NMDA and HCN1 receptors, ketamine has powerful analgesic properties. A systematic review showed that a single sub-anesthetic dose of intraoperative ketamine was associated with decreased visual analog pain scores up to 48 hours postoperatively.[37] At 24 hours postoperatively, ketamine was associated with an impressive 16 mg decrease in total morphine consumption.[37] Furthermore, adverse effects such as hallucinations were rarely reported when low dose ketamine was administered during general anesthesia.[37] Consistent with these findings, a Cochrane systematic review reported that sub-anesthetic doses of perioperative ketamine were associated with decreased postoperative pain, decreased morphine

consumption, and decreased nausea and vomiting.[38] Adverse effects were mild or absent.[38] An updated systematic review, which included 70 small studies involving 4,701 patients, recently confirmed that, in a dose-dependent manner, sub-anesthetic intraoperative ketamine was consistently associated with decreased postoperative pain despite decreased opioid consumption.[39] The more painful the surgical procedure, the greater was the analgesic benefit attributable to ketamine.[39] In keeping with decreased opioid consumption, postoperative nausea and vomiting were also less frequent in patients who received ketamine. However, patients who had been randomized to ketamine reported hallucinations and nightmares more frequently.[39] While efficacy data, based on numerous small studies, strongly suggest that supplementary ketamine should be used to decrease pain and opioid usage postoperatively, most practitioners have not incorporated low dose ketamine into their routine practice. Preliminary data gathered from 5 institutions (see below for details) involved in the PODCAST Trial suggest that, despite their knowledge regarding the analgesic and opioid-sparing effects, practitioners do not administer low-dose ketamine for pain because of concern for complications such as delirium. Thus, effectiveness data regarding the relationship of ketamine, delirium and pain are needed. Although numerous small efficacy studies have shown that ketamine decreases acute postoperative pain, its role in preventing persistent postoperative pain has not been rigorously explored. Many causal mechanisms that are thought to be implicated in persistent pain and a single intraoperative intervention might not be sufficient to decrease its occurrence. However, there have been encouraging findings about the potential of NMDA antagonists to decrease postoperative persistent pain. In the ENIGMA trial, patients were randomized to receive intraoperative oxygen with either nitrogen or nitrous oxide, which, like ketamine, is an NMDA antagonist. The investigators found that among those patients who received nitrous oxide, there was an absolute decrease in the percentage of patients who experience persistent pain (baseline incidence = 15%) at 3 months postoperatively of 7% (95% CI, 1.9% to 13.9%).[40] A randomized study has examined the potential beneficial effect of intraoperative ketamine on

persistent postoperative pain among patients undergoing total hip replacement.[41] This trial found a reduction in the ketamine group from 21% to 8% (reduction = 13%; 95% C.I., 1.3% to 24.9%) in patients experiencing persistent pain at 6 months after their surgery.[41] The PODCAST study would demonstrate whether sub-anesthetic dose intraoperative ketamine is effective at preventing acute postoperative pain in a real world setting. If ketamine were shown to have a substantial effect in decreasing acute postoperative pain, a next step would be to investigate rigorously its impact on persistent pain.

Current Utilization of Low-Dose Ketamine

A survey of anesthesia clinicians was conducted at five of the institutions (Washington University in St. Louis, University of Michigan, University of Manitoba, Weill Medical College of Cornell University, and Medical College of Wisconsin) participating in the PODCAST clinical trial. In total, 270 clinicians responded to the surveys; 18% (range among institutions 12% to 40%) of respondents currently incorporate adjunctive sub-anesthetic ketamine into their practice. Interestingly, 84% of survey respondents believe that low dose ketamine decreases acute postoperative pain, 81% feel that it decreases postoperative opioid consumption, and 51% believe that it decreases chronic postoperative pain. However, the reason that a minority of practitioners are currently administering adjunctive ketamine is probably because many remain concerned about the neurological side effects of even low dose ketamine; 68% of respondents expressed concern about hallucinations, 62% about delirium and 55% about nightmares.

Potential Impact of PODCAST

The PODCAST trial has a novel focus in that it is assessing the impact of an intervention (sub-anesthetic racemic ketamine administration) on both delirium and pain, two adverse and potentially linked outcomes that have not previously been jointly evaluated in a single large

clinical trial. Both delirium and pain are surprisingly common acute postoperative complications with major negative consequences for patients.[1,35] Currently, there are no official guidelines to screen patients for delirium and only few preventive measures have been investigated, with disappointing results. Since most patients with postoperative delirium have a hypoactive phenotype, it is frequently missed in clinical practice. As noted previously, postoperative delirium is associated with increased intensive care and hospital stay, with persistent cognitive decline and with increased mortality. Thus, any intervention that could decrease the incidence of postoperative delirium would probably have major positive implications for older patients undergoing surgical procedures. Unlike delirium, acute postoperative pain is routinely assessed and the Joint Commission has prioritized the prevention of severe postoperative pain as a universal goal. Unfortunately this objective has not been met, and both severe acute pain and debilitating chronic pain continue to afflict many surgical patients.[35,36] Of note, both pain and its treatment with opioid analgesics can be risk factors for delirium. Opioid analgesics are the mainstay therapy for postoperative pain, but their administration is curtailed in older patients particularly for safety considerations regarding respiratory depression, but also for concerns about causing sedation and delirium.

Pragmatic trials are intended to generate evidence of effectiveness of a test, treatment, procedure, or health-care service.[42,43] At present, there is a lack of pragmatic trials for candidate interventions to prevent important and common postoperative neurologic and psychiatric complications including delirium and pain. Ketamine is a plausible prophylactic option for each of these neurological and psychiatric complications. The American Society of Anesthesiologists has published Practice Guidelines for the management of acute and chronic pain, which, based on small efficacy or observational trials, include ketamine as a treatment option.[44,45] There are currently no guidelines for the prevention of postoperative delirium. Thus, a multicenter pragmatic trial comparing low dose ketamine with placebo is timely. It is important to emphasize

that any one of several potential results of the PODCAST trial will have important and immediate positive implications for older surgical patients. First ketamine might decrease both delirium and pain. This result would provide clear support for a larger comparative effectiveness trial testing ketamine as a prophylactic measure for both of these outcomes. Second, ketamine might decrease pain without increasing delirium. This result would provide compelling data that encourage the use of ketamine to prevent pain without concern for cognitive side effects such as delirium. Third, ketamine might decrease delirium and have no impact on pain. Although the lack of effect on pain is unlikely, this result would also encourage further study of the use of prophylactic intraoperative ketamine. However, low dose ketamine may be found to increase delirium, regardless of its impact on pain. This result would suggest that the incorporation of intraoperative ketamine into routine clinical practice for older surgical patients is not warranted and would negate the need for a larger pragmatic trial. Furthermore, the PODCAST trial will help determine ketamine dose-related effects by comparing two doses (0.5 mg/kg and 1 mg/kg) to placebo. As such, all of these potential results of the PODCAST trial have the potential to impact clinical practice and will be generalizable to all older surgical patients undergoing major surgical procedures because of the permissive inclusion criteria and the simplicity of intervention.[42]

METHODS AND ANALYSIS

Study design

PODCAST is a prospective randomized controlled trial has been designed in accordance with CONSORT guidelines[46] and will evaluate whether a single bolus dose of racemic ketamine (0.5 mg/kg or 1 mg/kg) following induction of anesthesia and before surgical incision decreases the incidence or severity of postoperative delirium and pain in a mixed elderly (>60 years) surgical patient population. Patients will undergo the standard preoperative anesthesia assessment.

Follow up information will be collected from the medical chart for up to 5 years. The overall study design is outlined in Figure 1.

Eligibility criteria

Patients 60 years old and older, who are competent to provide informed consent and who are undergoing major open cardiac surgery (e.g., coronary artery bypass graft, valve replacement) or non-cardiac surgeries (e.g., thoracic surgery, major vascular surgery, intra-abdominal surgery, open gynecologic surgery, open urologic surgery, major orthopedic surgery, hepato-biliary surgery and major ENT surgery) receiving general anesthesia will be eligible for inclusion. The exclusion criteria are based on the contraindications to ketamine from the 2005 ketamine package insert. Patients with an allergy to ketamine and those in whom a significant elevation of blood pressure would constitute a serious hazard (e.g., pheochromocytoma, aortic dissection) will be excluded. We shall also exclude patients with drug misuse history (e.g., ketamine, cocaine, heroin, amphetamine, methamphetamine, MDMA, phencyclidine, lysergic acid, mescaline, psilocybin), patients taking anti-psychotic medications (e.g., chlorpromazine, clozapine, olanzapine, risperidone, haloperidol, quetiapine, paliperidone, amisulpride, sertindole), and patients with a weight outside the range 50 kg – 200 kg (110 lbs – 440 lbs). Patients will be enrolled either during a preoperative clinic visit or in the hospital prior to surgery.

Baseline Assessment

At the time of enrollment, patients will undergo the same delirium and pain evaluation that will be used postoperatively (see Outcomes section). Additionally patients will be screened for functional dependence using the Barthel Index of Activities of Daily Living,[47] for depression using the patient health questionnaire (PHQ-8),[48] and for obstructive sleep apnea using the STOP-Bang criteria.[49] Patients will be asked if they have a history of delirium, and if this

presented after surgery. They will also be asked about any falls they have experienced in the six months prior to surgery. Comorbid conditions, including the components of the Charlson Comorbidity Index,[50] will be obtained by reviewing the patients' medical records. Any available preoperative lab results, including electrolytes and blood counts, will also be recorded.

Interventions

As this is a pragmatic trial, apart from administration of the study drug (ketamine or normal saline), all decisions about anesthetic technique will be made by the anesthetic team assigned to each patient. The only exception is that clinicians will be instructed not to administer any ketamine other than the study drug. The intention of this trial is to interfere as little as possible with the usual process of care, which will increase the applicability of the findings.[43] Following induction of general anesthesia, an intravenous dose of 0.5 mg/kg racemic ketamine, 1 mg/kg racemic ketamine, or an equivalent volume of normal saline will be injected via a reliable (free flowing) central or peripheral intravenous line. Clinicians will be blinded to the treatment arm of the study. Anesthetic factors such as the use of nitrous oxide, protocols for pain prevention, use of neuraxial anesthesia, use of nerve blocks, and other practices that could potentially affect primary or secondary outcomes will be assessed in a *post hoc* manner.

Outcomes

Primary outcomes

Trained members of the research team who are blinded to the treatment arm of the study will assess patients for **delirium** (primary outcome) using the Confusion Assessment Method (CAM)[51] and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[52,53] for patients who are unable to speak (e.g., have a tracheal tube or tracheostomy) on the intensive

care unit. These methods (the CAM and the CAM-ICU) have been shown to be reliable and to have good agreement with the DSM-IV criteria for delirium.[53-55] Delirium assessments will be performed when patients can be aroused sufficiently in order to be assessed for delirium (Richmond Agitation and Sedation Score > -4). The first delirium assessment will be attempted if feasible on the day of surgery in the afternoon / evening. Patients will then be assessed for delirium twice daily (from postoperative day 1 to postoperative day 3) in the morning and in the afternoon / evening with at least 6 hours between assessments. Each patient will be assessed for delirium up to seven times. At the Washington University site, the patients' family members will perform the Family Confusion Assessment Method (FAM-CAM) separately from the investigators performing their assessments.[56] Investigators and family members will be blinded to each other's assessments. The FAM-CAM has demonstrated high sensitivity and specificity for detection of delirium and good agreement with the CAM[56], but has not been specifically evaluated in the postoperative setting. After the final delirium assessment, patients will complete the Delirium and Pain Self-Assessment Questionnaire (Appendix A). Incident delirium subsequent to this period is unlikely to be directly related to anesthetic or other intraoperative factors.

Secondary outcomes

Study team members blinded to the treatment group of the patient will assess all secondary outcomes. **Acute pain** (secondary outcome) will be assessed prior to surgery and then postoperatively by using the Behavioral Pain Scale (BPS)[57] or the Behavioral Pain Scale for the Non-Intubated patient (BPS-NI)[58] and the 10-cm VAS (Visual Analog Scale) at the same times as patients are assessed for delirium. The BPS-NI has been shown to be a valid and reliable tool for measuring pain in a predominantly delirious patient population.[58] Interviewers will rate the BPS or BPS-NI prior to asking the patient to complete the VAS to prevent bias in the BPS

and BPS-NI assessments. Postoperative daily amount of opioids and sedatives administered will be ascertained from the patient's electronic health record spanning the period after surgery until the final delirium assessment is complete. After the final delirium assessment, patients will complete the Delirium and Pain Self-Assessment Questionnaire (Appendix A). **Postoperative nausea and vomiting** (secondary outcome) will be assessed at the same time points that patients are assessed for delirium by asking patients to rate the severity of their nausea and vomiting, if present, on a three point scale (mild, moderate, severe). Patients will be questioned at each assessment about side effects, especially hallucinations and nightmares. Intensive care unit and hospital length of stay will be obtained from the patient's medical record. At some of the participating sites in the PODCAST trial, patients will receive a survey, which will be sent by mail or email one month following surgery. This survey will collect patient reported outcomes (PROs) on depressive symptoms, affect, persistent pain, functionality and quality of life. Depressive symptoms will be assessed with the eight item Patient Health Questionnaire (PHQ-8), Affect will be assessed with two 10-item mood scales that comprise the Positive and Negative Affect Schedule (PANAS) within three to six months postoperatively.[59] The same screens for depressive symptoms and affect will also be conducted in the hospital on postoperative day 3. Persistent pain will be assessed with the Brief Pain Inventory Short Form (BPI-SF). The Barthel Index will be used to report functionality and quality of life will be assessed from the Veteran's Rand-12 (VR-12) questionnaire.

Standardization of training and outcomes assessment

All study team members who perform delirium assessments will undergo a rigorous training process. For the initial training, representatives from each study site participated in a full-day training program led by Dr. Sharon Inouye, the original creator of the CAM. Those who attended this initial training will oversee the training of other team members at their sites.

Trainees must demonstrate competence at both conducting CAM interviews and in scoring these interviews. For the initial part of training, trainees must conduct at least two satisfactory CAM interviews in the presence of a trained team member. These interviews will not be on patients enrolled in the PODCAST trial. To establish their ability to score CAM interviews reliably, trainees will accompany trained team members to conduct CAM interviews. A trained member of the research team will conduct each CAM interview for patients enrolled in the PODCAST trial. The trainee will observe the interview, but will score the CAM independently. The trainee must agree with the trainer on the presence or absence of all twelve cognitive features assessed by the CAM on a minimum of two delirious and two non-delirious patients. After meeting the stipulations of training, the newly trained team member will conduct their first interview of a patient enrolled into the PODCAST trial in the presence of a previously trained team member.

Assessment of the standardization and reliability of delirium assessments

After training, all PODCAST team members administering delirium assessments will be invited to participate in a project to demonstrate the validity and reliability of the CAM in our study population. Participants will view and rate eight videos of standard interviews depicting delirious and non-delirious patients. Participants will independently score the CAM for each scenario. Demographic information, level of education, level of clinical experience, and primary language will also be collected from all participants. Data will be de-identified. All scores and data will be submitted to the lead site, Washington University. The group's scores will then be compared to determine the reliability of delirium assessments across sites. Additionally, the group's scores will be compared to a set of "gold standard" scores for the videos (determined by Dr. Inouye's team) This comparison is intended to demonstrate validity of the CAM in our study setting.

Overall, the goal of the project is to demonstrate standardization of the delirium outcome across all study sites.

Sample size

Based on published delirium incidences in the scientific literature (Table 1), we estimate conservatively that the incidence of postoperative delirium in a mixed major surgical population of older patients will be between 20% and 25%. Based on data from a sub-study of the BAG-RECALL trial that we have recently completed, the incidence of delirium among patients admitted to our cardiothoracic intensive care unit at Barnes-Jewish Hospital is 25% within three postoperative days. Hudetz et al found that ketamine was associated with a 28% (95% CI, 8% to 46%) absolute risk reduction in delirium (from a baseline incidence of 31%).[27] A 28% reduction is likely to be an over-optimistic effect size for designing a pragmatic study; 10% is more realistic as the most optimistic effect size and remains consistent with the confidence interval for the effect size found by Hudetz et al.[27] Assuming a two-sided type I error rate of 5%, a sample size of 600 will give greater than 80% power to detect a decrease in the incidence of delirium from 25% to 15% with ketamine. On the other hand, we consider the minimum clinically important difference (MCID) or effect size to be 2%, which corresponds to a number needed to treat of 50 surgical patients to prevent one episode of delirium. The rationale for the low MCID is that delirium is a serious postoperative complication that is associated with increased mortality and the proposed intervention (low dose ketamine) is safe, inexpensive and not likely to have adverse effects.

There are two specific issues to clarify in this study: i) the likely effect size with ketamine; and ii) the optimal ketamine dose. Ketamine might increase delirium, decrease delirium or have no impact on delirium. If ketamine increases delirium, it is more likely to increase delirium at a higher dose (1 mg/kg). If ketamine decreases delirium, it might have a dose response effect –

less delirium at the higher ketamine dose (1 mg/kg). We anticipate that ketamine will decrease pain in a dose dependent manner – 1mg/kg will be superior to 0.5 mg/kg. Accrual of 200 patients to each dose of ketamine along with a placebo arm will allow a more robust assessment of the dose-response efficacy for postoperative analgesia than previous studies with fewer numbers. In general, the higher ketamine dose might have more side effects. As such, this trial might inform whether the higher ketamine dose can be used, in view of its possibly superior analgesia, with a potential benefit in relation to delirium and without excessive side effects. The dosage determination going forward will depend on the observed incidence of delirium with each dose, analgesia efficacy with each dose, and side effect profile with each dose. The proposed design for the study is shown in Table 2.

Group	**N**
Placebo	200 patients
Ketamine Low Dose (0.5 mg/kg)	200 patients
Ketamine Moderate Dose (1 mg/kg)	200 patients

Table 2: Patient Allocation.

With this approach, we believe that this study will clearly inform whether it is indicated, both in terms of efficacy and in terms of feasibility, to pursue a larger study. The purpose of the larger study (PODCAST2) will be to determine definitively whether ketamine is associated with a reduction in delirium (and pain) in high-risk older surgical patients, without incurring an increase in side effects. As the main effect evaluated will be whether ketamine decreases delirium, Table 3 provides a useful guide for the potential findings of the current study with their implications.

Delirium Incidence in Placebo Groups (N=200)	**Delirium Incidence in Ketamine Groups (N=400)**	**Effect Size (Reduction in delirium with**	**95% Confidence Interval (CI) for Effect Size**

		ketamine)	
25% (N=50)	25% (N=100)	0%	-7.6% to 7.1%
Implication: Consider Pursuing a larger study only if pain is decreased in ketamine groups, and there is no increase in side effects.			
25% (N=50)	22.5% (N=90)	2.5%	-4.5% to 10.0%
Implication: Although the point estimate is >2% (MCID), a 9,500 patient study would be required to clarify more precisely the effectiveness of ketamine in preventing delirium. Other outcomes in the study (e.g., pain reduction and side effects) would inform the approach.			
25% (N=50)	20% (N=80)	5%	-1.9% to 12.4%
Implication: Pursue larger study with approximately 2,500 patients to clarify more precisely the effect of ketamine on preventing delirium.			
25% (N=50)	17.5% (N=70)	7.5%	0.7% to 14.8%
Implication: Pursue larger study (approximately 1,200 patients) to clarify whether effect size >2% (MCID) and to define it more precisely.			
25%	15%	10%	3.3% to 17.1%
Implication: For main effect, lower bound of CI >2% (MCID). Ketamine's benefit in decreasing delirium is very likely, but a larger study (approximately 1,200 patients) would define its effect more precisely.			

Table 3: Potential Findings of PODCAST.

Recruitment

This clinical trial will be conducted at Washington University in St. Louis and other sites. Our research team has conducted large randomized, controlled trials, which enrolled (approximately) 2,000 patients over 14 months in the B-unaware trial,[60] 6,000 patients over 26 months in the BAG-RECALL trial[59] and 22,000 patients over 24 months in the Michigan Awareness Control Study.[61] Based on the inclusion criteria and the number of eligible surgical patients, we estimate that one year will be sufficient for patient enrollment to the proposed trial, and a further one year for data analysis.

Allocation

Subjects will be block randomized by the hospital pharmacy departments in groups of 15 (1:1:1 ratio - 0.5 mg/kg ketamine: 1 mg/kg ketamine: placebo), stratified by site, in order to keep the randomization balanced and the groups more homogeneous. The outcome of this random assignment will be concealed from the study team and all study subjects and trial staff will be blinded to the randomization. Codes will be held by the hospital pharmacies and they will dispense medication. Randomization codes will remain concealed until the primary analysis is completed. Prepared syringes of either placebo or ketamine will be directly delivered to the operating room in which surgery of the consented patient will take place as soon as the research team informs the pharmacy about the patient going to the operating room for surgery.

Data analysis and management

Data analysis for this investigation will require comparisons of patient outcomes (e.g., delirium, pain, length of stay, adverse events) in the three study groups to assess for significant differences among ketamine doses (placebo, 0.5 mg/kg and 1 mg/kg). For proportions and categorical outcomes, such as incident delirium, we will use the chi square test (or Fisher's exact test in the case of sparse data) to compare proportions across the three groups and the Cochran-Armitage test to test for dose response trends. For continuous outcomes, such as visual analog pain scores and opioid consumption, we will use repeated–measures analysis of variance tests to detect the main effects. The Tukey post-hoc test will also be run on all significant interactions to determine differences between individual and combined groups (e.g., placebo versus combined ketamine groups; 0.5 mg/kg ketamine versus 1 mg/kg ketamine). For multivariate analyses, we will apply the Cox proportional-hazards model for recurrent events to

investigate the effects of low doses of intraoperative ketamine on delirium by comparing its occurrence and timing across the study groups. We will also model the number of postoperative delirium incidents using a Poisson hurdle regression to find out the difference in the proportion of patients with and without delirium, and for those who experience delirium, the difference in its recurrence. Both models (Cox proportional-hazards and hurdle model) will account for differences in ketamine effectiveness in cardiac versus non-cardiac surgery by including interaction terms for ketamine dose and cardiac surgery status, while adjusting for other influential variables. We will also use mixed-effects regression models to assess differences among the subgroups in continuous outcome variables over time (e.g., postoperative pain scores and opioid consumption). These models will likewise account for interactions between ketamine dose and cardiac surgery status. All statistical testing will be two sided, and p values <0.05 will be regarded as significant. No interim analyses are planned. Appropriate adjustment will be made for multiple analyses.

The Division of Biostatistics Informatics Core at Washington University will be used as a central location for data processing and management. Washington University belongs to a consortium of institutional partners that work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Division of Biostatistics Informatics Core. The iterative development and testing process result in a well-planned data collection strategy for individual studies. REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics at Washington University. All web-based information transmission is encrypted. The data is all stored on a private, firewall protected network. All users are given individual user ids and passwords and their access is restricted on a role-specific basis.

REDCap was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Washington University guidelines. REDCap currently supports >500 academic/non-profit consortium partners on six continents and 38,800 research end-users.[62]

Monitoring

The research team will monitor the study for adverse events. All serious adverse events will be reported to the IRB according to IRB stipulations. The monitoring plan for this study is appropriate for the planned pragmatic trial. As an anesthetic drug, ketamine has an excellent safety profile and record. In particular, low dose ketamine (0.5 mg/kg or 1 mg/kg) administered prior to surgical incision is unlikely to be associated with major adverse events, and even minor side effects manifesting after induction of anesthesia and the start of surgery are improbable.[37,38,63]

The PODCAST trial will have an appropriate data and safety monitoring plan for a low risk clinical trial. There will be a charter to guide the functions of the Data Safety and Monitoring Board (DSMB), and the DSMB will produce reports in accordance with NIH guidelines. The DSMB will provide independent oversight of the PODCAST trial and will review general conduct of the trial as well as study data for participant safety.[64] The DSMB will be comprised of independent, multidisciplinary experts who will make recommendations regarding the continuation, modification, or termination of the trial.[65] The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments to which the patients have consented to participate, and to assure the regulatory bodies and the public (and possibly funding agencies) that conflicts of interest do not compromise either patient safety or trial integrity.[66] There will be no pre-specified interim analysis given the size of this study; frequent analyses might increase the likelihood of bias.[64] There will be a provision for early stoppage for safety concerns, but not for efficacy or for futility.[64] Trials that stop early for

benefit show implausibly large treatment effects, particularly when the number of events is small.[67] Truncated trials have been associated with greater effect sizes than trials not stopped early, independent of the presence of statistical stopping rules.[68]

All members of the DSMB will be at the Washington University site. Local investigators at all participating sites will report serious adverse events, or unanticipated problems involving risks to subjects or others, to their IRB and to the PI of the study at Washington University. If such problems are considered related to the trial, then they will also be reported to IRBs at other participating sites and to the chairperson of the DSMB. The members of the DSMB will have no direct involvement in the conduct of the PODCAST trial. Neither will they have financial, proprietary or professional conflicts of interest, which may affect the impartial, independent decision-making responsibilities of the DSMB.[64,65] Letters of invitation to prospective DSMB members will include the following: “Acceptance of this invitation to serve on the PODCAST DSMB confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest.” All DSMB members will sign a Conflict of Interest Certification to confirm no conflict exists. There will be between three and eight people on the DSMB, in order to optimize performance.[69] The DSMB will be advisory rather than executive on the basis that it is the PODCAST trial investigators who are ultimately responsible for the conduct of the trial.[69]

The risks associated with this study are low. There is a rare risk of breach of confidentiality. In contrast to other anesthetics, protective reflexes such as coughing and swallowing are maintained with low dose ketamine. The 2005 package insert for ketamine reports the induction dose for anesthesia as follows: The initial dose of ketamine administered intravenously may range from 1 mg/kg to 4.5 mg/kg. The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg. The short-term side effects of ketamine at higher

doses (>1-2 mg/kg) than the dosages proposed for this study (0.5 mg/kg or 1 mg/kg) include tachycardia, nystagmus, hypersalivation, euphoria, emergence reactions, hallucinations and nightmares.[70] It is possible, but very unlikely, that low dose ketamine (0.5 mg/kg or 1 mg/kg) administered just after induction of anesthesia or administration of sedative medications will cause these side effects.[37,38,63] Emergence reactions, hallucinations and nightmares are more common in younger patients receiving ketamine. In published studies on low dose ketamine (0.25 to 1 mg/kg) administered during general anesthesia, side effects have generally not been found.[37] The main side effects that might occur are nightmares and hallucinations. Other neuropsychiatric side effects might occur, most likely within the first 24 hours after surgery, and will be determined from patient interviews. The incidence of these side effects in this patient population is currently unknown, and thus side effects will be reported separately and jointly. Meta-analysis suggests that ketamine might be associated with an increase in neurologic and psychiatric side effects from approximately 5% to 7.5%. This study will be >80% powered to detect an increase in side effects from 5% to 12% and 20% powered to detect an increase in side effects from approximately 5% to 7.5%. As part of the informed consent process for this study, patients will be informed of the rare risks and will be asked about them after their surgery. In the unlikely event that serious side effects occur, they will be documented and will be reported to the human research protection office and to the study's DSMB. Participants will not incur any study-related expenses, nor will they be financially compensated for their participation.

Ethics and dissemination

Ethics approval and consent

The PODCAST trial has been approved by the institutional review boards of the principal investigators' home institutions (Washington University, St. Louis and University of Michigan, Ann Arbor). Institutional review board approval has also been obtained at some of the

participating sites (Postgraduate Institute of Medical Education and Research, Chandigarh, India; University of Manitoba, Winnipeg, Canada; Weill Medical College, Cornell University, New York City; Medical College of Wisconsin, Milwaukee) and is ongoing at other sites. Recruitment began in February of 2014 and will continue through 2015. Potential participants will be approached for enrollment by a member of the research team who will explain the purpose of the study and written informed consent will be obtained for all participants. Patients may choose not to participate in this study and there will be no penalty in terms of the care that they receive.

Confidentiality

Necessary protected health information will only be shared with members of the research team. To help protect confidentiality, research charts will be stored in a locked cabinet inside the locked research office. Electronic data and demographic information will also be kept in a password-protected electronic database stored on the departmental network drive and only accessible via password-protected departmental computers. A member of the research team will enter this information. Code numbers, rather than names, will appear on any data and documents used for evaluation or statistical analyses.

Dissemination

Dissemination plans include presentations at local, national and international scientific conferences. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript.

CONCLUSIONS

In the next four decades, the US population over the age of 60 is predicted to double to more than 80 million individuals. The aging population often requires surgery, which can be

frequently complicated by postoperative pain and delirium. Delirium is defined as an acute brain dysfunction that presents as fluctuating levels of inattention and disordered thinking, and has been reported to affect up to 70% of surgical patients older than 60. Likewise, severe postoperative pain continues to affect a large proportion of surgical patients, especially the elderly, and is another major contributor to delirium. Unfortunately, opioid medications, the current standard for analgesia, can themselves lead to delirium and other adverse consequences. Clinicians therefore face the paradox that both pain and the mainstay treatment of pain can lead to delirium. Although causal relationships have not been established, postoperative delirium is associated with increased intensive care unit and hospital stay, persistent cognitive decline, and increased mortality rate. What is needed is a therapeutic intervention that can both attenuate pain and decrease the occurrence of delirium. Mounting evidence suggests that the intraoperative administration of low dose (i.e., sub-anesthetic) ketamine, an anesthetic drug that has been in common use for 50 years, prevents delirium, lessens the severity of postoperative pain, and has an opioid-sparing effect. These multiple beneficial effects have been attributed to ketamine's anti-inflammatory and anti-excitotoxic actions. Despite these benefits, low-dose intraoperative ketamine currently does not enjoy widespread adoption, primarily because clinicians are concerned that the psychoactive properties of ketamine might compromise postoperative cognition. The PODCAST randomized controlled trial intends to address a gap in the field through an international, multicenter study that tests the effectiveness of ketamine in reducing both delirium and pain in surgical patients older than 60.

AUTHORS' CONTRIBUTORSHIP

Michael Avidan and George Mashour are the primary authors of the PODCAST protocol. Their contributions include drafting and editing the protocol, conceptualizing the study design, and organizing conduct across all sites. Bradley Fritz contributed to the PODCAST trial by editing the protocol, conceptualizing study design, creating the electronic database, REDCap used for data collection, and co-authoring a manual of operations for study conduct. Hannah Maybrier contributed to PODCAST by editing the protocol, co-authoring the manual of operations, recruiting patients for enrollment, collecting data, and coordinating the study across all sites. Maxwell Muench contributed to PODCAST by co-authoring a manual of operations, recruiting patients for enrollment, and collecting data. Krisztina Escallier contributed to PODCAST by editing the protocol, conceptualizing study design, and co-authoring a manual of operations. Yulong Chen contributed to PODCAST by editing the protocol and conceptualizing study design. Arbi Ben Abdallah contributed to PODCAST by editing the protocol and conceptualizing study design, including the statistical modelling of the study. Sharon Inouye contributed PODCAST by training investigators to perform delirium assessments and conceptualizing study design. Stephen Choi, Robert Downey, Hilary Grocott, Gyujeong Noh, Judith Hudetz, Eric Jacobsohn, Heiko Kaiser, Paul Pagel, Kane Pryor, Ryan Pong, Robert Veselis, and Virendra Kumar Arya contributed to PODCAST by editing the study protocol, conceptualizing study design, recruiting participants, and collecting data.

All authors including Avidan, Mashour, Fritz, Maybrier, Muench, Escallier, Chen, Ben Abdallah, Inouye, Veselis, Grocott, Hudetz, Pryor, Pagel, Arya, Pong, Jacobsohn, Gyujeong, Kaiser, Downey, and Choi have critically revised the PODCAST protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the PODCAST trial.

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COMPETING INTERESTS

None of the authors have conflicts of interest to disclose.

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The Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) Study: Protocol for an International Multicenter Randomized Controlled Trial

Trial Registration: NCT01690988 (last updated December, 2013)

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WORLD HEALTH ORGANIZATION DATA SET

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Public Title	The Prevention of Delirium and Complications After Surgical Treatment (PODCAST) Study
Scientific Title	The Prevention of Delirium and Complications After Surgical Treatment (PODCAST) Study: a randomized controlled trial
Countries of Recruitment	United States, Canada, Switzerland, India, South Korea

Health Condition(s) or Problem(s) Studied	Postoperative delirium, postoperative pain, and postoperative nausea and vomiting
Intervention(s)	Study arm 1: 0.5 mg/kg of ketamine diluted to 20 mL with saline given intravenously after anesthetic induction and before surgical incision. Study arm 2: 1 mg/kg of ketamine diluted to 20 mL with saline given intravenously after anesthetic induction and before surgical incision Placebo: 20 mL of saline solution given intravenously after anesthetic induction and before surgical incision.
Key Inclusion Criteria and Exclusion Criteria	Ages eligible for study: ≥ 60 years Sexes eligible for study: both Healthy volunteers: no Inclusion criteria: patients 60 years or older undergoing major open surgery receiving general anesthesia Exclusion criteria: allergy to ketamine, pheochromocytoma, aortic dissection, intracranial hemorrhage, intracranial mass, history of hypertensive emergency, uncontrolled glaucoma, history of drug misuse (e.g., ketamine, cocaine, heroin, amphetamine, methamphetamine, MDMA, phencyclidine, lysergic acid, mescaline, psilocybin), currently taking anti-psychotic medications (e.g., chlorpromazine, clozapine, olanzapine, risperidone, haloperidol, quetiapine, paliperidone, amisulpride, sertindole), weight <50 kg (110 lbs) or >200 kg (440 lbs).
Study Type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double blind (subject, healthcare providers, investigator, research personnel) Assignment: single arm Primary purpose: prevention Phase III
Date of First Enrollment	February 2014

Target Sample Size	600
Recruitment Status	Recruiting
Primary Outcome(s)	Outcome name: postoperative delirium Method of measurement: Confusion Assessment Method or Confusion Assessment Method for the ICU Time points of interest: two hours post-operation, mornings and evenings of postoperative days one through three
Key Secondary Outcomes	Outcome name: postoperative pain Method of measurement: Visual Analog Scale and Behavioral Pain Scale or Behavioral Pain Scale – Non-Intubated Time points of interest: two hours post-operation, mornings and evenings of postoperative days one through three Outcome name: postoperative nausea and vomiting Method of measurement: patient self-report as present or absent and degree of severity (mild, moderate, or severe). Time points of interest: two hours post-operation, mornings and evenings of postoperative days one through three

ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

Principal Investigators:
Michael Avidan, MBBCh
George Mashour, MD, PhD

Responsibilities include: design and conduct of PODCAST trial, preparation of protocol and revisions, organizing steering committee meetings, and publication of study reports.

Steering Committee:

Michael Avidan, MBBCh	Eric Jacobsohn, MBBCh	Kane Pryor, MD
Daniel Emmert, MD, PhD	Hilary Grocott, MD	Gyujeong Noh, MD, PhD
Robert Veselis, MD	Stephen Choi, MD	Paul Pagel, MD, PhD
Sharon Inouye, MD, MPH	Ryan Pong, MD	Judith Hudetz, PhD
George Mashour, MD, PhD	Virendra Kumar Arya, MD	Milo Engoren, MD
Robert Downey, MD	Heiko Kaiser, MD	

Responsibilities include: agreement of final protocol, recruitment of patients and coordinating with principle investigator, reviewing progress of study and if necessary, changes to the protocol.

Trial Management Committee:
Michael Avidan, MBBCh
George Mashour, MD, PhD
Hannah Maybrier

Responsibilities include: study planning, organization of steering committee meetings, provides annual risk report to the Human Research Protection Office at Washington University, reports SAEs (Serious Adverse Events) to Washington University IRB (Institutional Review Board), responsible for maintenance of electronic database, REDCap, advice for lead investigators, assistance with international review, ethics committee applications, data verification, and randomization of study participants

Lead Investigators:

Michael Avidan, MBBCh	Eric Jacobsohn, MBBCh	Kane Pryor, MD
Daniel Emmert, MD, PhD	Hilary Grocott, MD	Gyujeong Noh, MD, PhD
Robert Veselis, MD	Stephen Choi, MD	Paul Pagel, MD, PhD
Sharon Inouye, MD, MPH	Ryan Pong, MD	Judith Hudetz, PhD
George Mashour, MD, PhD	Virendra Kumar Arya, MD	Milo Engoren, MD
Robert Downey, MD	Heiko Kaiser, MD	

Responsibilities include: identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol.

Data and Safety Monitoring Committee:
Arbi Ben Abdallah, PhD
Michael Avidan, MBBCh
Charlie Hantler, MD
Simon Haroutounian, PhD

Responsibilities include: reviewing and evaluating the study data to ensure participant safety, study conduct, progress, and efficacy, and making recommendations regarding the continuation, modification, and termination of the trial.

PROTOCOL VERSIONS

June 18, 2012	Original
April 25, 2013	Amendment 01: Changes to study aims: - Changed specific aim 1: removed associated adverse events, such as ICU stay, hospital stay, and mortality - Changed specific aim 2: removed assessing symptoms of other chronic neuropsychiatric processes (such as depression and posttraumatic stress). - Changed specific aim 3: testing the effects of ketamine on postoperative depression and stress to attenuating postoperative inflammation. Amendment 02: Addition of study arm. Patients are randomized to one of three study arms: 0.5 mg/kg ketamine, 1 mg/kg ketamine, or placebo dose of equal volume Amendment 03: Removed phrase that patients will be contacted between 1 and 3 months after surgery to ask about quality of life, lasting pain, feelings of depression or stress. Amendment 04: Removed phrase that patients will be contacted 1 year after surgery to ask about quality of life and mental function. Amendment 05: Changed inclusion criteria to patients older than 60 years (was 65 years) Amendment 06: Removal of phrase regarding study of ketamine use with posttraumatic stress disorder. Amendment 07: Addition of phrase that hypothesis is based on published data of reduced pain and opioid consumption after surgery. The study will resolve gap in the field by further assessing chronic pain Amendment 09: Addition of phrase that discusses delirium and pain as two adverse and potentially linked outcomes that have not been previously jointly evaluated in a large clinical trial.
May 30, 2013	Amendment 01: Removal of specific aim 3: testing whether ketamine improves postoperative inflammation
January 3, 2014	Amendment 01: Addition of weight criterion to Exclusion Criteria; weight < 50 kg (110 lb.) and > 200 kg (440 lb.) are excluded. Amendment 02: Addition of justification of sample size. Included statement that when assuming a two sided type one error of 5% the sample size of 600 patients will detect decrease in delirium from

25% to 15% with the use of ketamine with a power greater than 80%.

Amendment 03: Change in randomization protocol. We will not randomize cardiac and non-cardiac surgery patients separately.

Amendment 04: Omission of one of the points of clarification of the pilot study – to determine the efficacy of ketamine in cardiac vs. non-cardiac surgery.

Amendment 05: Changes to baseline assessments. Addition of Confusion Assessment Method (CAM), Behavioral Pain Scale – Non-Intubated (BPS-NI), Visual Analog Scale (VAS), Barthel Index, Patient Health Questionnaire-8 (PHQ-8), STOP-Bang, and questions about falls.

Amendment 06: Addition of medical record review screening for comorbid conditions included in the Charlson Comorbidity Index and lab values including electrolytes and blood counts.

Amendment 07: Addition of the statement that clinicians are instructed not to give enrolled patients ketamine as part of their anesthetic technique.

Amendment 08: Addition of mailed survey sent 30 days postoperatively assessing depression, positive and negative affect, quality of life, functional independence, and pain using the PROMIS v1.0 – Emotional Distress – Depression, Positive and Negative Affect Scale (PANAS), Veteran's Rand-12 (VR-12), Barthel Index, and the Brief Pain Inventory Short Form (BPI-SF), respectively.

Amendment 09: Addition of Family Confusion Assessment Method (FAM-CAM) at Washington University, a tool in which family members will assess patient's behavior and determine if delirium is suggested.

Amendment 10: Addition of observational tools used to assess pain: BPS, BPS-NI

Amendment 11: Addition of postoperative nausea and vomiting as a secondary outcome.

Amendment 12: Addition of description of delirium assessment training.

Amendment 13: Addition of statement that REDCap (Research Electronic Data Capture) will be used.

Amendment 14: Addition of statement saying there are no planned interim analyses.

	Amendment 15: Changes in statistical analysis: - Cox proportional-hazards model for recurrent events used to determine the effects of low-dose ketamine on the occurrence and duration of delirium across study groups. - Poisson hurdle regression used to determine the differences in patients with delirium and those without delirium, and the differences in recurrence in the patient population that does experience delirium. - Both Poisson and Cox will also be used to compare effects of ketamine on cardiac vs. non-cardiac surgery patients. - Cochran-Armitage test to determine dose-response trends - Mixed-effects regression model to detect differences of continuous outcome variables in subgroups. Amendment 16: Addition of list of short- and long-term side effects of ketamine
March 7, 2014	Amendment 01: Addition of Patient Health Questionnaire 8 (PHQ 8) for baseline assessments and postoperative day three assessments. This replaced the PROMIS depression screen. We would like to assess depression using the same tool at all time points. Amendment 02: Collection of patient's email at baseline. Patients have the option to receive the 30 day survey by mail or email. Amendment 03: Addition of Figure 1: Study Flow Chart. This is a visual representation of study conduct.

ABSTRACT

Introduction: Postoperative delirium is one of the most common complications of major surgery, affecting 10-70% of surgical patients 60 years and older. Delirium is an acute change in cognition that manifests as poor attention and illogical thinking, and is associated with longer ICU and hospital stay, long-lasting cognitive deterioration, and increased mortality. Ketamine has been used as an anesthetic drug for over 50 years and has an established safety record. Recent research suggests that, in addition to preventing acute postoperative pain, a sub-anesthetic dose of intraoperative ketamine could decrease the incidence of postoperative delirium as well as other neurologic and psychiatric outcomes. However, these proposed benefits of ketamine have not been tested in a large clinical trial.

Methods: The PODCAST study is an international, multicenter, randomized controlled trial. Six hundred cardiac and major non-cardiac surgery patients will be randomized to receive ketamine (0.5 mg/kg or 1 mg/kg) or placebo following anesthetic induction and prior to surgical incision. For the primary outcome, blinded observers will assess delirium on the day of surgery (postoperative day 0) and twice daily from postoperative days 1 to 3 using the Confusion Assessment Method or the Confusion Assessment Method for the ICU. For the secondary outcomes, blinded observers will estimate pain using the Behavioral Pain Scale or the Behavioral Pain Scale for Non-Intubated Patients and patient self-report.

Ethics and dissemination: The PODCAST trial has been approved by the ethics boards of five participating institutions; approval is ongoing at other sites. Recruitment began in February 2014 and will~~is expected to~~ continue through 2016~~5~~. Dissemination plans

include presentations at scientific conferences, scientific publications, stakeholder engagement and popular media.

Registration details: The study is registered at clinicaltrials.gov, NCT01690988 (last updated December, 2013).

The PODCAST trial is being conducted under the auspices of the Neurological Outcomes Network for Surgery (NEURONS).

STRENGTHS:

- The effects of ketamine are being observed in the routine clinical setting.
- Because PODCAST is a multicenter international trial, the results of the study will potentially be generalizable.
- This trial has a novel focus of assessing delirium and pain concurrently. Results could reveal that these two outcomes are potentially linked in the postoperative setting.
- PODCAST is a randomized, controlled double-blinded study.
- Investigators assessing for delirium have been appropriately trained and will use reliable and validated assessment tools.

LIMITATIONS:

- Pain is a subjective experience and is therefore difficult to measure.
- The Visual Analog Scale (VAS) is not a validated pain assessment instrument in delirious patients. In an attempt to mitigate this limitation, pain will also be assessed

observationally using the Behavioral Pain Scale (BPS) and the Behavioral Pain Scale – Non-intubated (BPS-NI).

- Delirium is fluctuating in nature. Because patients will be assessed at discrete time points, it is possible that some episodes of delirium will not be detected.

INTRODUCTION

Background and rationale

Delirium

Postoperative delirium is one of the most common complications of major surgery and affects between 10% and 70% of all surgical patients older than 60 years (Table 1).[1] The estimated additional healthcare costs associated with delirium exceed $60,000 per patient per year.[2] While causal relationships have not been established, delirium is associated with increased morbidity and mortality, prolonged length of hospital and intensive care unit (ICU) stay, functional and cognitive decline with nursing home or long-term care facility placement.[3-6] Furthermore, the acute deterioration in cognition and psychomotor agitation frequently seen with delirium is often distressing for both patients and their families.

Surgery type	Study (year)	Population	Delirium Rate	Detection method
Unselected	Radtke[7]	Recovery room after elective general anesthesia	9.9%	Nu-DESC
Surgical ICU	Pandharipande[8]	Surgical ICU	73%	CAM-ICU
		Trauma ICU	67%	
Head and neck	Weed[9]	Major head and neck	17%	Not stated
Cardiac	Kazmierski[10]	Cardiac surgery with CPB	Age <60: 16.3% Age ≥60: 24.7%	DSM-IV
	Rudolph[11]	Patients >60 undergoing elective or urgent cardiac surgery	43%	CAM
	Saczynski[12]	Patients >60 undergoing elective coronary artery bypass grafting or valve replacement surgery	46%	CAM
Vascular	Marcantonio,[13] Schneider,[14] Bohner,[15] and Benoit[16]	Abdominal aortic aneurysm repair	33-54%	CAM or DSM-IV

	Schneider,[14] and Bohner[15]	Peripheral vascular	30-48%	DSM-IV
Orthopedic	Fisher[17]	Patients >60 undergoing elective orthopedic procedures	17.5%	CAM
	Marcantonio[18] and Lee[19]	Patients >65 undergoing emergent hip fracture repair	30.2-41%	CAM

Table 1: Incidence of Delirium in Major Surgeries. CAM, Confusion Assessment Method; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ICU, Intensive Care Unit; Nu-DESC, The Nursing Delirium Screening Scale

The diagnostic criteria for delirium have recently been updated in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Delirium is an acute neurocognitive disorder characterized by a fluctuating level of consciousness with impairment of attention and cognition. In the postoperative context, delirium typically manifests between 0 and 96 hours following the surgical intervention. It is unclear why postoperative delirium occurs so frequently. Age greater than 60, male gender, history of dementia or depression, sensory impairment, and chronic medical illness are consistently described as risk factors for delirium.[20] No effective prophylactic or curative treatments for postoperative delirium have been identified.

Ketamine and Delirium

Ketamine is an anesthetic agent that has been in common use for more than 50 years. Ketamine has a wide margin of safety, and as of 2005 had been studied in over 12,000 operative and diagnostic procedures, involving over 10,000 patients from 105 separate studies (Ketamine package insert 2005). There is a pharmacological rationale for using ketamine as a preventative measure against postoperative delirium based on its N-methyl-D-aspartate (NMDA) antagonism.[21] Normally, excitatory amino acids such as glutamate and aspartate act as agonists at NMDA receptors, and, in the setting of surgery and inflammation, they might

promote excitotoxic injury and apoptosis.[21] As an NMDA antagonist, ketamine has the potential to protect against such neurological injury.[22] Ketamine has also been posited to inhibit HCN1 receptors, which mediate the hyperpolarization-activated cation current.[23] Such inhibition is pertinent to delirium because HCN1 channels are important for regulating states of consciousness[24] and are up-regulated by inflammation.[25] HCN1 receptors are also thought to play a critical role in neuropathic pain through inflammatory cascades.[26]

Based on the pharmacological rationale for neuroprotection, a 58-patient randomized, controlled trial was conducted to determine whether ketamine might prevent delirium after major cardiac surgery.[27] There was a significant reduction in postoperative delirium from 31% to 3% with the administration of low dose ketamine (0.5 mg/kg) upon induction of anesthesia. While encouraging, this trial must be regarded as preliminary owing to its small sample size, and single center design. Interestingly, the same investigators also found that ketamine was associated with improved cognition beyond the immediate postoperative period.[28] Differences between the ketamine and placebo groups were evident in tests of nonverbal memory, verbal memory, and executive function. The investigators found that C reactive protein, a non-specific inflammatory marker, was similar at baseline in the ketamine and the placebo groups. On the first postoperative day, C reactive protein was elevated in both groups, but was significantly higher in the placebo group. The investigators hypothesized that the neuroprotective effect of ketamine might have been, in part, attributable to its anti-inflammatory actions.[28] In support of the plausibility of this hypothesis, ketamine use in another cardiac surgical population was similarly shown to attenuate postoperative increases in inflammatory markers.[29]

Intraoperative sub-anesthetic dose ketamine is appealing as a potential preventative intervention for delirium, since it is inexpensive and has an excellent safety profile. A number of questions remain to be answered regarding postoperative delirium. Despite the fact that delirium is a common and serious postoperative complication, intraoperative factors contributing to pathogenesis have not been rigorously investigated, and only a few small trials have been

conducted examining interventions to decrease its incidence. It is also currently unknown whether postoperative delirium is preventable, particularly in patients with underlying vulnerabilities. Importantly, ketamine in higher (anesthetic) doses has become less popular over time owing to side effects, including hallucinations and emergence reactions, especially in younger patients.[30,31] To ensure treatment effectiveness, the preliminary results identifying sub-anesthetic dose ketamine as a useful preventative intervention for postoperative delirium should therefore be confirmed or refuted using a large scale, pragmatic, randomized controlled trial design prior to routine adoption of low dose ketamine for this purpose.

Acute and Persistent Pain

Similar to delirium, both acute and persistent pain are common postoperative complications, with a negative impact on patients' lives. The Joint Commission has established the prevention of severe postoperative pain as a benchmark of quality,[32] and adequate pain management is increasingly viewed as a fundamental human right.[33,34] Unfortunately, this standard of care has not been attained to date; it has previously been estimated that about a third of patients suffer severe acute postsurgical pain following major procedures.[35] Furthermore, patients who have acute postoperative pain are more likely to develop chronic pain, and the incidence of persistent postoperative pain following major surgeries remains between 5% and 30%.[36] As an antagonist at NMDA and HCN1 receptors, ketamine has powerful analgesic properties. A systematic review showed that a single sub-anesthetic dose of intraoperative ketamine was associated with decreased visual analog pain scores up to 48 hours postoperatively.[37] At 24 hours postoperatively, ketamine was associated with an impressive 16 mg decrease in total morphine consumption.[37] Furthermore, adverse effects such as hallucinations were rarely reported when low dose ketamine was administered during general anesthesia.[37] Consistent with these findings, a Cochrane systematic review reported that sub-anesthetic doses of perioperative ketamine were associated with decreased postoperative pain, decreased morphine

consumption, and decreased nausea and vomiting.[38] Adverse effects were mild or absent.[38] An updated systematic review, which included 70 small studies involving 4,701 patients, recently confirmed that, in a dose-dependent manner, sub-anesthetic intraoperative ketamine was consistently associated with decreased postoperative pain despite decreased opioid consumption.[39] The more painful the surgical procedure, the greater was the analgesic benefit attributable to ketamine.[39] In keeping with decreased opioid consumption, postoperative nausea and vomiting were also less frequent in patients who received ketamine. However, patients who had been randomized to ketamine reported hallucinations and nightmares more frequently.[39] While efficacy data, based on numerous small studies, strongly suggest that supplementary ketamine should be used to decrease pain and opioid usage postoperatively, most practitioners have not incorporated low dose ketamine into their routine practice. Preliminary data gathered from 5 institutions (see below for details) involved in the PODCAST Trial suggest that, despite their knowledge regarding the analgesic and opioid-sparing effects, practitioners do not administer low-dose ketamine for pain because of concern for complications such as delirium. Thus, effectiveness data regarding the relationship of ketamine, delirium and pain are needed. Although numerous small efficacy studies have shown that ketamine decreases acute postoperative pain, its role in preventing persistent postoperative pain has not been rigorously explored. Many causal mechanisms that are thought to be implicated in persistent pain and a single intraoperative intervention might not be sufficient to decrease its occurrence. However, there have been encouraging findings about the potential of NMDA antagonists to decrease postoperative persistent pain. In the ENIGMA trial, patients were randomized to receive intraoperative oxygen with either nitrogen or nitrous oxide, which, like ketamine, is an NMDA antagonist. The investigators found that among those patients who received nitrous oxide, there was an absolute decrease in the percentage of patients who experience persistent pain (baseline incidence = 15%) at 3 months postoperatively of 7% (95% CI, 1.9% to 13.9%).[40] A randomized study has examined the potential beneficial effect of intraoperative ketamine on

persistent postoperative pain among patients undergoing total hip replacement.[41] This trial found a reduction in the ketamine group from 21% to 8% (reduction = 13%; 95% C.I., 1.3% to 24.9%) in patients experiencing persistent pain at 6 months after their surgery.[41] The PODCAST study would demonstrate whether sub-anesthetic dose intraoperative ketamine is effective at preventing acute postoperative pain in a real world setting. If ketamine were shown to have a substantial effect in decreasing acute postoperative pain, a next step would be to investigate rigorously its impact on persistent pain.

Current Utilization of Low-Dose Ketamine

A survey of anesthesia clinicians was conducted at five of the institutions (Washington University in St. Louis, University of Michigan, University of Manitoba, Weill Medical College of Cornell University, and Medical College of Wisconsin) participating in the PODCAST clinical trial. In total, 270 clinicians responded to the surveys; 18% (range among institutions 12% to 40%) of respondents currently incorporate adjunctive sub-anesthetic ketamine into their practice. Interestingly, 84% of survey respondents believe that low dose ketamine decreases acute postoperative pain, 81% feel that it decreases postoperative opioid consumption, and 51% believe that it decreases chronic postoperative pain. However, the reason that a minority of practitioners are currently administering adjunctive ketamine is probably because many remain concerned about the neurological side effects of even low dose ketamine; 68% of respondents expressed concern about hallucinations, 62% about delirium and 55% about nightmares.

Potential Impact of PODCAST

The PODCAST trial has a novel focus in that it is assessing the impact of an intervention (sub-anesthetic- racemic ketamine administration) on both delirium and pain, two adverse and potentially linked outcomes that have not previously been jointly evaluated in a single large

clinical trial. Both delirium and pain are surprisingly common acute postoperative complications with major negative consequences for patients.[1,35] Currently, there are no official guidelines to screen patients for delirium and only few preventive measures have been investigated, with disappointing results. Since most patients with postoperative delirium have a hypoactive phenotype, it is frequently missed in clinical practice. As noted previously, postoperative delirium is associated with increased intensive care and hospital stay, with persistent cognitive decline and with increased mortality. Thus, any intervention that could decrease the incidence of postoperative delirium would probably have major positive implications for older patients undergoing surgical procedures. Unlike delirium, acute postoperative pain is routinely assessed and the Joint Commission has prioritized the prevention of severe postoperative pain as a universal goal. Unfortunately this objective has not been met, and both severe acute pain and debilitating chronic pain continue to afflict many surgical patients.[35,36] Of note, both pain and its treatment with opioid analgesics can be risk factors for delirium. Opioid analgesics are the mainstay therapy for postoperative pain, but their administration is curtailed in older patients particularly for safety considerations regarding respiratory depression, but also for concerns about causing sedation and delirium.

Pragmatic trials are intended to generate evidence of effectiveness of a test, treatment, procedure, or health-care service.[42,43] At present, there is a lack of pragmatic trials for candidate interventions to prevent important and common postoperative neurologic and psychiatric complications including delirium and pain. Ketamine is a plausible prophylactic option for each of these neurological and psychiatric complications. The American Society of Anesthesiologists has published Practice Guidelines for the management of acute and chronic pain, which, based on small efficacy or observational trials, include ketamine as a treatment option.[44,45] There are currently no guidelines for the prevention of postoperative delirium. Thus, a multicenter pragmatic trial comparing low dose ketamine with placebo is timely. It is important to emphasize

that any one of several potential results of the PODCAST trial will have important and immediate positive implications for older surgical patients. First ketamine might decrease both delirium and pain. This result would provide clear support for a larger comparative effectiveness trial testing ketamine as a prophylactic measure for both of these outcomes. Second, ketamine might decrease pain without increasing delirium. This result would provide compelling data that encourage the use of ketamine to prevent pain without concern for cognitive side effects such as delirium. Third, ketamine might decrease delirium and have no impact on pain. Although the lack of effect on pain is unlikely, this result would also encourage further study of the use of prophylactic intraoperative ketamine. However, low dose ketamine may be found to increase delirium, regardless of its impact on pain. This result would suggest that the incorporation of intraoperative ketamine into routine clinical practice for older surgical patients is not warranted and would negate the need for a larger pragmatic trial. Furthermore, the PODCAST trial will help determine ketamine dose-related effects by comparing two doses (0.5 mg/kg and 1 mg/kg) to placebo. As such, all of these potential results of the PODCAST trial have the potential to impact clinical practice and will be generalizable to all older surgical patients undergoing major surgical procedures because of the permissive inclusion criteria and the simplicity of intervention.[42]

METHODS AND ANALYSIS

Study design

PODCAST is a prospective randomized controlled trial has been designed in accordance with CONSORT guidelines[46] and will evaluate whether a single bolus dose of racemic ketamine (0.5 mg/kg or 1 mg/kg) following induction of anesthesia and before surgical incision decreases the incidence or severity of postoperative delirium and pain in a mixed elderly (>60 years) surgical patient population. Patients will undergo the standard preoperative anesthesia assessment.

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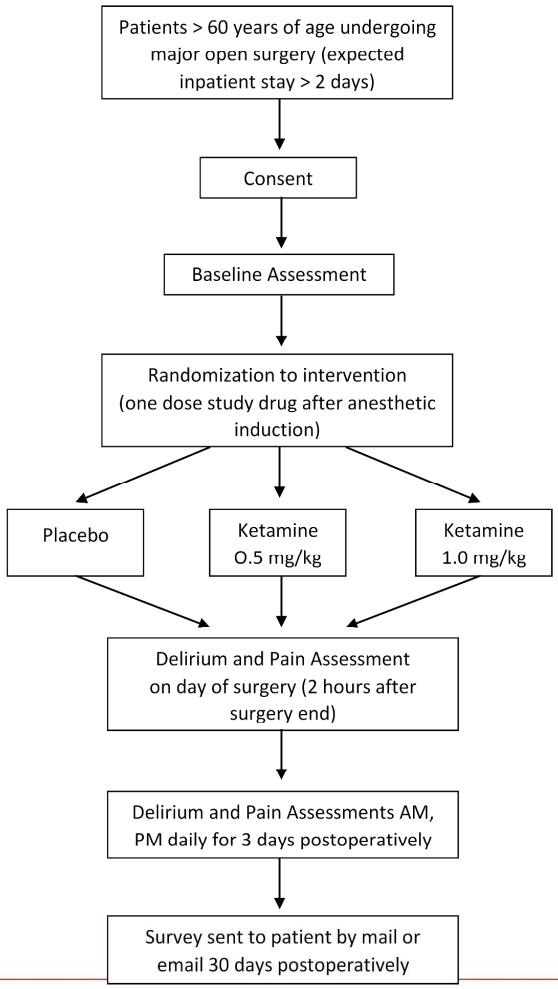
Follow up information will be collected from the medical chart for up to 5 years. The overall study design is outlined in Figure 1.



~~Figure 1: Study Enrollment~~

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Eligibility criteria

Patients 60 years old and older, who are competent to provide informed consent and who are undergoing major open cardiac surgery (e.g., coronary artery bypass graft, valve replacement) or non-cardiac surgeries (e.g., thoracic surgery, major vascular surgery, intra-abdominal surgery, open gynecologic surgery, open urologic surgery, major orthopedic surgery, hepato-biliary surgery and major ENT surgery) receiving general anesthesia will be eligible for inclusion. The exclusion criteria are based on the contraindications to ketamine from the 2005 ketamine package insert. Patients with an allergy to ketamine and those in whom a significant elevation of blood pressure would constitute a serious hazard (e.g., pheochromocytoma, aortic dissection) will be excluded. We shall also exclude patients with drug misuse history (e.g., ketamine, cocaine, heroin, amphetamine, methamphetamine, MDMA, phencyclidine, lysergic acid, mescaline, psilocybin), patients taking anti-psychotic medications (e.g., chlorpromazine, clozapine, olanzapine, risperidone, haloperidol, quetiapine, paliperidone, amisulpride, sertindole), and patients with a weight outside the range 50 kg – 200 kg (110 lbs – 440 lbs). Patients will be enrolled either during a preoperative clinic visit or in the hospital prior to surgery.

Baseline Assessment

At the time of enrollment, patients will undergo the same delirium and pain evaluation that will be used postoperatively (see Outcomes section). Additionally patients will be screened for functional dependence using the Barthel Index of Activities of Daily Living,[47] for depression using the patient health questionnaire (PHQ-8),[48] and for obstructive sleep apnea using the STOP-Bang criteria.[49] Patients will be asked if they have a history of delirium, and if this presented after surgery. They will also be asked about any falls they have experienced in the six months prior to surgery. Comorbid conditions, including the components of the Charlson Comorbidity Index,[50] will be obtained by reviewing the patients' medical records. Any available preoperative lab results, including electrolytes and blood counts, will also be recorded.

Interventions

As this is a pragmatic trial, apart from administration of the study drug (ketamine or normal saline), all decisions about anesthetic technique will be made by the anesthetic team assigned to each patient. The only exception is that clinicians will be instructed not to administer any ketamine other than the study drug. The intention of this trial is to interfere as little as possible with the usual process of care, which will increase the applicability of the findings.[43] Following induction of general anesthesia, an intravenous dose of 0.5 mg/kg racemic ketamine, 1 mg/kg racemic ketamine, or an equivalent volume of normal saline will be injected via a reliable (free flowing) central or peripheral intravenous line. Clinicians will be blinded to the treatment arm of the study. Anesthetic factors such as the use of nitrous oxide, protocols for pain prevention, use of neuraxial anesthesia, use of nerve blocks, and other practices that could potentially affect primary or secondary outcomes will be assessed in a *post hoc* manner.

Outcomes

Primary outcomes

Trained members of the research team who are blinded to the treatment arm of the study will assess patients for **delirium** (primary outcome) using the Confusion Assessment Method (CAM)[51] and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[52,53] for patients who are unable to speak (e.g., have a tracheal tube or tracheostomy) on the intensive care unit. These methods (the CAM and the CAM-ICU) have been shown to be reliable and to have good agreement with the DSM-IV criteria for delirium.[53-55] Delirium assessments will be performed when patients can be aroused sufficiently in order to be assessed for delirium (Richmond Agitation and Sedation Score > -4). The first delirium assessment will be attempted if feasible on the day of surgery in the afternoon / evening. Patients will then be assessed for delirium twice daily (from postoperative day 1 to postoperative day 3) in the morning and in the

afternoon / evening with at least 6 hours between assessments. Each patient will be assessed for delirium up to seven times. At the Washington University site, the patients' family members will perform the Family Confusion Assessment Method (FAM-CAM) separately from the investigators performing their assessments.[56] Investigators and family members will be blinded to each other's assessments. The FAM-CAM has demonstrated high sensitivity and specificity for detection of delirium and good agreement with the CAM[56], but has not been specifically evaluated in the postoperative setting. After the final delirium assessment, patients will complete the Delirium and Pain Self-Assessment Questionnaire (Appendix A). Incident delirium subsequent to this period is unlikely to be directly related to anesthetic or other intraoperative factors.

Secondary outcomes

Study team members blinded to the treatment group of the patient will assess all secondary outcomes. **Acute pain** (secondary outcome) will be assessed prior to surgery and then postoperatively by using the Behavioral Pain Scale (BPS)[57] or the Behavioral Pain Scale for the Non-Intubated patient (BPS-NI)[58] and the 10-cm VAS (Visual Analog Scale) ~~(Appendix E and F)~~ at the same times as patients are assessed for delirium. The BPS-NI has been shown to be a valid and reliable tool for measuring pain in a predominantly delirious patient population.[58] Interviewers will rate the BPS or BPS-NI prior to asking the patient to complete the VAS to prevent bias in the BPS and BPS-NI assessments. Postoperative daily amount of opioids and sedatives administered will be ascertained from the patient's electronic health record spanning the period after surgery until the final delirium assessment is complete. After the final delirium assessment, patients will complete the Delirium and Pain Self-Assessment Questionnaire (Appendix A). **Postoperative nausea and vomiting** (secondary outcome) will be assessed at the same time points that patients are assessed for delirium by asking patients to rate the

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severity of their nausea and vomiting, if present, on a three point scale (mild, moderate, severe). Patients will be questioned at each assessment about side effects, especially hallucinations and nightmares. Intensive care unit and hospital length of stay will be obtained from the patient's medical record. At some of the participating sites in the PODCAST trial, patients will receive a survey, which will be sent by mail or email one month following surgery. This survey will collect patient reported outcomes (PROs) on depressive symptoms, affect, persistent pain, functionality and quality of life. Depressive symptoms will be assessed with the eight item Patient Health Questionnaire (PHQ-8), Affect will be assessed with two 10-item mood scales that comprise the Positive and Negative Affect Schedule (PANAS) within three to six months postoperatively.[59] The same screens for depressive symptoms and affect will also be conducted in the hospital on postoperative day 3. Persistent pain will be assessed with the Brief Pain Inventory Short Form (BPI-SF). The Barthel Index will be used to report functionality and quality of life will be assessed from the Veteran's Rand-12 (VR-12) questionnaire.

Standardization of training and outcomes assessment

All study team members who perform delirium assessments will undergo a rigorous training process. For the initial training, representatives from each study site participated in a full-day training program led by Dr. Sharon Inouye, the original creator of the CAM. Those who attended this initial training will oversee the training of other team members at their sites. Trainees must demonstrate competence at both conducting CAM interviews and in scoring these interviews. For the initial part of training, trainees must conduct at least two satisfactory CAM interviews in the presence of a trained team member. These interviews will not be on patients enrolled in the PODCAST trial. To establish their ability to score CAM interviews reliably, trainees will accompany trained team members to conduct CAM interviews. A trained member of the research team will conduct each CAM interview for patients enrolled in the

PODCAST trial. The trainee will observe the interview, but will score the CAM independently. The trainee must agree with the trainer on the presence or absence of all twelve cognitive features assessed by the CAM on a minimum of two delirious and two non-delirious patients. After meeting the stipulations of training, the newly trained team member will conduct their first interview of a patient enrolled into the PODCAST trial in the presence of a previously trained team member.

Assessment of the standardization and reliability of delirium assessments

After training, all PODCAST team members administering delirium assessments will be invited to participate in a project to demonstrate the validity and reliability of the CAM in our study population. Participants will view and rate eight videos of standard interviews depicting delirious and non-delirious patients. Participants will independently score the CAM for each scenario. Demographic information, level of education, level of clinical experience, and primary language will also be collected from all participants. Data will be de-identified. All scores and data will be submitted to the lead site, Washington University. The group's scores will then be compared to determine the reliability of delirium assessments across sites. Additionally, the group's scores will be compared to a set of "gold standard" scores for the videos (determined by Dr. Inouye's team) This comparison is intended to demonstrate validity of the CAM in our study setting. Overall, the goal of the project is to demonstrate standardization of the delirium outcome across all study sites.

Sample size

Based on published delirium incidences in the scientific literature (Table 1), we estimate conservatively that the incidence of postoperative delirium in a mixed major surgical population

of older patients will be between 20% and 25%. Based on data from a sub-study of the BAG-RECALL trial that we have recently completed, the incidence of delirium among patients admitted to our cardiothoracic intensive care unit at Barnes-Jewish Hospital is 25% within three postoperative days. Hudetz et al found that ketamine was associated with a 28% (95% CI, 8% to 46%) absolute risk reduction in delirium (from a baseline incidence of 31%).[27] A 28% reduction is likely to be an over-optimistic effect size for designing a pragmatic study; 10% is more realistic as the most optimistic effect size and remains consistent with the confidence interval for the effect size found by Hudetz et al.[27] Assuming a two-sided type I error rate of 5%, a sample size of 600 will give greater than 80% power to detect a decrease in the incidence of delirium from 25% to 15% with ketamine. On the other hand, we consider the minimum clinically important difference (MCID) or effect size to be 2%, which corresponds to a number needed to treat of 50 surgical patients to prevent one episode of delirium. The rationale for the low MCID is that delirium is a serious postoperative complication that is associated with increased mortality and the proposed intervention (low dose ketamine) is safe, inexpensive and not likely to have adverse effects.

There are two specific issues to clarify in this study: i) the likely effect size with ketamine; and ii) the optimal ketamine dose. Ketamine might increase delirium, decrease delirium or have no impact on delirium. If ketamine increases delirium, it is more likely to increase delirium at a higher dose (1 mg/kg). If ketamine decreases delirium, it might have a dose response effect – less delirium at the higher ketamine dose (1 mg/kg). We anticipate that ketamine will decrease pain in a dose dependent manner – 1mg/kg will be superior to 0.5 mg/kg. Accrual of 200 patients to each dose of ketamine along with a placebo arm will allow a more robust assessment of the dose-response efficacy for postoperative analgesia than previous studies with fewer numbers. In general, the higher ketamine dose might have more side effects. As such, this trial might inform whether the higher ketamine dose can be used, in view of its

possibly superior analgesia, with a potential benefit in relation to delirium and without excessive side effects. The dosage determination going forward will depend on the observed incidence of delirium with each dose, analgesia efficacy with each dose, and side effect profile with each dose. The proposed design for the study is shown in Table 2.

Group	N
Placebo	200 patients
Ketamine Low Dose (0.5 mg/kg)	200 patients
Ketamine Moderate Dose (1 mg/kg)	200 patients

Table 2: Patient Allocation.

With this approach, we believe that this study will clearly inform whether it is indicated, both in terms of efficacy and in terms of feasibility, to pursue a larger study. The purpose of the larger study (PODCAST2) will be to determine definitively whether ketamine is associated with a reduction in delirium (and pain) in high-risk older surgical patients, without incurring an increase in side effects. As the main effect evaluated will be whether ketamine decreases delirium, Table 3 provides a useful guide for the potential findings of the current study with their implications.

Delirium Incidence in Placebo Groups (N=200)	Delirium Incidence in Ketamine Groups (N=400)	Effect Size (Reduction in delirium with ketamine)	95% Confidence Interval (CI) for Effect Size
25% (N=50)	25% (N=100)	0%	-7.6% to 7.1%
Implication: Consider Pursuing a larger study only if pain is decreased in ketamine groups, and there is no increase in side effects.			
25% (N=50)	22.5% (N=90)	2.5%	-4.5% to 10.0%
Implication: Although the point estimate is >2% (MCID), a 9,500 patient study would be required to			

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clarify more precisely the effectiveness of ketamine in preventing delirium. Other outcomes in the study (e.g., pain reduction and side effects) would inform the approach.			
25% (N=50)	20% (N=80)	5%	-1.9% to 12.4%
Implication: Pursue larger study with approximately 2,500 patients to clarify more precisely the effect of ketamine on preventing delirium.			
25% (N=50)	17.5% (N=70)	7.5%	0.7% to 14.8%
Implication: Pursue larger study (approximately 1,200 patients) to clarify whether effect size >2% (MCID) and to define it more precisely.			
25%	15%	10%	3.3% to 17.1%
Implication: For main effect, lower bound of CI >2% (MCID). Ketamine's benefit in decreasing delirium is very likely, but a larger study (approximately 1,200 patients) would define its effect more precisely.			

Table 3: Potential Findings of PODCAST.

Recruitment

This clinical trial will be conducted at Washington University in St. Louis and other sites. Our research team has conducted large randomized, controlled trials, which enrolled (approximately) 2,000 patients over 14 months in the B-unaware trial,[60] 6,000 patients over 26 months in the BAG-RECALL trial[59] and 22,000 patients over 24 months in the Michigan Awareness Control Study.[61] Based on the inclusion criteria and the number of eligible surgical patients, we estimate that one year will be sufficient for patient enrollment to the proposed trial, and a further one year for data analysis.

Allocation

Subjects will be block randomized by the hospital pharmacy departments in groups of 15 (1:1:1 ratio - 0.5 mg/kg ketamine: 1 mg/kg ketamine: placebo), stratified by site, in order to keep the randomization balanced and the groups more homogeneous. The outcome of this random

assignment will be concealed from the study team and all study subjects and trial staff will be blinded to the randomization. Codes will be held by the hospital pharmacies and they will dispense medication. Randomization codes will remain concealed until the primary analysis is completed. Prepared syringes of either placebo or ketamine will be directly delivered to the operating room in which surgery of the consented patient will take place as soon as the research team informs the pharmacy about the patient going to the operating room for surgery.

Data analysis and management

Data analysis for this investigation will require comparisons of patient outcomes (e.g., delirium, pain, length of stay, adverse events) in the three study groups to assess for significant differences among ketamine doses (placebo, 0.5 mg/kg and 1 mg/kg). For proportions and categorical outcomes, such as incident delirium, we will use the chi square test (or Fisher's exact test in the case of sparse data) to compare proportions across the three groups and the Cochran-Armitage test to test for dose response trends. For continuous outcomes, such as visual analog pain scores and opioid consumption, we will use repeated–measures analysis of variance tests to detect the main effects. The Tukey post-hoc test will also be run on all significant interactions to determine differences between individual and combined groups (e.g., placebo versus combined ketamine groups; 0.5 mg/kg ketamine versus 1 mg/kg ketamine). For multivariate analyses, we will apply the Cox proportional-hazards model for recurrent events to investigate the effects of low doses of intraoperative ketamine on delirium by comparing its occurrence and timing across the study groups. We will also model the number of postoperative delirium incidents using a Poisson hurdle regression to find out the difference in the proportion of patients with and without delirium, and for those who experience delirium, the difference in its recurrence. Both models (Cox proportional-hazards and hurdle model) will account for differences in ketamine effectiveness in cardiac versus non-cardiac surgery by including

interaction terms for ketamine dose and cardiac surgery status, while adjusting for other influential variables. We will also use mixed-effects regression models to assess differences among the subgroups in continuous outcome variables over time (e.g., postoperative pain scores and opioid consumption). These models will likewise account for interactions between ketamine dose and cardiac surgery status. All statistical testing will be two sided, and p values <0.05 will be regarded as significant. No interim analyses are planned. Appropriate adjustment will be made for multiple analyses.

The Division of Biostatistics Informatics Core at Washington University will be used as a central location for data processing and management. Washington University belongs to a consortium of institutional partners that work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Division of Biostatistics Informatics Core. The iterative development and testing process result in a well-planned data collection strategy for individual studies. REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics at Washington University. All web-based information transmission is encrypted. The data is all stored on a private, firewall protected network. All users are given individual user ids and passwords and their access is restricted on a role-specific basis. REDCap was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Washington University guidelines. REDCap currently supports >500 academic/non-profit consortium partners on six continents and 38,800 research end-users.[62]

Monitoring

The research team will monitor the study for adverse events. All serious adverse events will be reported to the IRB according to IRB stipulations. The monitoring plan for this study is appropriate for the planned pragmatic trial. As an anesthetic drug, ketamine has an excellent safety profile and record. In particular, low dose ketamine (0.5 mg/kg or 1 mg/kg) administered prior to surgical incision is unlikely to be associated with major adverse events, and even minor side effects manifesting after induction of anesthesia and the start of surgery are improbable.[37,38,63]

The PODCAST trial will have an appropriate data and safety monitoring plan for a low risk clinical trial. There will be a charter to guide the functions of the Data Safety and Monitoring Board (DSMB), and the DSMB will produce reports in accordance with NIH guidelines. The DSMB will provide independent oversight of the PODCAST trial and will review general conduct of the trial as well as study data for participant safety.[64] The DSMB will be comprised of independent, multidisciplinary experts who will make recommendations regarding the continuation, modification, or termination of the trial.[65] The members will have the requisite expertise to examine accumulating data, to protect the integrity of the clinical experiments to which the patients have consented to participate, and to assure the regulatory bodies and the public (and possibly funding agencies) that conflicts of interest do not compromise either patient safety or trial integrity.[66] There will be no pre-specified interim analysis given the size of this study; frequent analyses might increase the likelihood of bias.[64] There will be a provision for early stoppage for safety concerns, but not for efficacy or for futility.[64] Trials that stop early for benefit show implausibly large treatment effects, particularly when the number of events is small.[67] Truncated trials have been associated with greater effect sizes than trials not stopped early, independent of the presence of statistical stopping rules.[68]

All members of the DSMB will be at the Washington University site. Local investigators at all participating sites will report serious adverse events, or unanticipated problems involving risks to subjects or others, to their IRB and to the PI of the study at Washington University. If such problems are considered related to the trial, then they will also be reported to IRBs at other participating sites and to the chairperson of the DSMB. The members of the DSMB will have no direct involvement in the conduct of the PODCAST trial. Neither will they have financial, proprietary or professional conflicts of interest, which may affect the impartial, independent decision-making responsibilities of the DSMB.[64,65] Letters of invitation to prospective DSMB members will include the following: "Acceptance of this invitation to serve on the PODCAST DSMB confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." All DSMB members will sign a Conflict of Interest Certification to confirm no conflict exists. There will be between three and eight people on the DSMB, in order to optimize performance.[69] The DSMB will be advisory rather than executive on the basis that it is the PODCAST trial investigators who are ultimately responsible for the conduct of the trial.[69]

The risks associated with this study are low. There is a rare risk of breach of confidentiality. In contrast to other anesthetics, protective reflexes such as coughing and swallowing are maintained with low dose ketamine. The 2005 package insert for ketamine reports the induction dose for anesthesia as follows: The initial dose of ketamine administered intravenously may range from 1 mg/kg to 4.5 mg/kg. The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg. The short-term side effects of ketamine at higher doses (>1-2 mg/kg) than the dosages proposed for this study (0.5 mg/kg or 1 mg/kg) include tachycardia, nystagmus, hypersalivation, euphoria, emergence reactions, hallucinations and nightmares.[70] It is possible, but very unlikely, that low dose ketamine (0.5 mg/kg or 1 mg/kg) administered just after induction of anesthesia or administration of sedative medications will

cause these side effects.[37,38,63] Emergence reactions, hallucinations and nightmares are more common in younger patients receiving ketamine. In published studies on low dose ketamine (0.25 to 1 mg/kg) administered during general anesthesia, side effects have generally not been found.[37] The main side effects that might occur are nightmares and hallucinations. Other neuropsychiatric side effects might occur, most likely within the first 24 hours after surgery, and will be determined from patient interviews. The incidence of these side effects in this patient population is currently unknown, and thus side effects will be reported separately and jointly. Meta-analysis suggests that ketamine might be associated with an increase in neurologic and psychiatric side effects from approximately 5% to 7.5%. This study will be >80% powered to detect an increase in side effects from 5% to 12% and 20% powered to detect an increase in side effects from approximately 5% to 7.5%. As part of the informed consent process for this study, patients will be informed of the rare risks and will be asked about them after their surgery. In the unlikely event that serious side effects occur, they will be documented and will be reported to the human research protection office and to the study's DSMB. Participants will not incur any study-related expenses, nor will they be financially compensated for their participation.

Ethics and dissemination

Ethics approval and consent

The PODCAST trial has been approved by the institutional review boards of the principal investigators' home institutions (Washington University, St. Louis and University of Michigan, Ann Arbor). Institutional review board approval has also been obtained at some of the participating sites (Postgraduate Institute of Medical Education and Research, Chandigarh, India; University of Manitoba, Winnipeg, Canada; Weill Medical College, Cornell University, New York City; Medical College of Wisconsin, Milwaukee) and is ongoing at other sites. Recruitment ~~is anticipated to~~ began in February of 2014 and will continue through 2015. Potential

participants will be approached for enrollment by a member of the research team who will explain the purpose of the study and written informed consent will be obtained for all participants. Patients may choose not to participate in this study and there will be no penalty in terms of the care that they receive.

Confidentiality

Necessary protected health information will only be shared with members of the research team. To help protect confidentiality, research charts will be stored in a locked cabinet inside the locked research office. Electronic data and demographic information will also be kept in a password-protected electronic database stored on the departmental network drive and only accessible via password-protected departmental computers. A member of the research team will enter this information. Code numbers, rather than names, will appear on any data and documents used for evaluation or statistical analyses.

Dissemination

Dissemination plans include presentations at local, national and international scientific conferences. There are no publication restrictions and no professional writers will be involved in the generation of the manuscript.

CONCLUSIONS

In the next four decades, the US population over the age of 60 is predicted to double to more than 80 million individuals. The aging population often requires surgery, which can be frequently complicated by postoperative pain and delirium. Delirium is defined as an acute brain dysfunction that presents as fluctuating levels of inattention and disordered thinking, and has been reported to affect up to 70% of surgical patients older than 60. Likewise, severe

postoperative pain continues to affect a large proportion of surgical patients, especially the elderly, and is another major contributor to delirium. Unfortunately, opioid medications, the current standard for analgesia, can themselves lead to delirium and other adverse consequences. Clinicians therefore face the paradox that both pain and the mainstay treatment of pain can lead to delirium. Although causal relationships have not been established, postoperative delirium is associated with increased intensive care unit and hospital stay, persistent cognitive decline, and increased mortality rate. What is needed is a therapeutic intervention that can both attenuate pain and decrease the occurrence of delirium. Mounting evidence suggests that the intraoperative administration of low dose (i.e., sub-anesthetic) ketamine, an anesthetic drug that has been in common use for 50 years, prevents delirium, lessens the severity of postoperative pain, and has an opioid-sparing effect. These multiple beneficial effects have been attributed to ketamine's anti-inflammatory and anti-excitotoxic actions. Despite these benefits, low-dose intraoperative ketamine currently does not enjoy widespread adoption, primarily because clinicians are concerned that the psychoactive properties of ketamine might compromise postoperative cognition. The PODCAST randomized controlled trial intends to address a gap in the field through an international, multicenter study that tests the effectiveness of ketamine in reducing both delirium and pain in surgical patients older than 60.

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AUTHORS' CONTRIBUTORSHIP

Michael Avidan and George Mashour are the primary authors of the PODCAST protocol. Their contributions include drafting and editing the protocol, conceptualizing the study design, and organizing conduct across all sites. Bradley Fritz contributed to the PODCAST trial by editing the protocol, conceptualizing study design, creating the electronic database, REDCap used for data collection, and co-authoring a manual of operations for study conduct. Hannah Maybrier contributed to PODCAST by editing the protocol, co-authoring the manual of operations, recruiting patients for enrollment, collecting data, and coordinating the study across all sites. Maxwell Muench contributed to PODCAST by co-authoring a manual of operations, recruiting patients for enrollment, and collecting data. Krisztina Escallier contributed to PODCAST by editing the protocol, conceptualizing study design, and co-authoring a manual of operations. Yulong Chen contributed to PODCAST by editing the protocol and conceptualizing study design. Arbi Ben Abdallah contributed to PODCAST by editing the protocol and conceptualizing study design, including the statistical modelling of the study. Sharon Inouye contributed PODCAST by training investigators to perform delirium assessments and conceptualizing study design. Stephen Choi, Robert Downey, Hilary Grocott, Gyujeong Noh, Judith Hudetz, Eric Jacobsohn, Heiko Kaiser, Paul Pagel, Kane Pryor, Ryan Pong, Robert Veselis, and Virendra Kumar Arya contributed to PODCAST by editing the study protocol, conceptualizing study design, recruiting participants, and collecting data.

All authors including Avidan, Mashour, Fritz, Maybrier, Muench, Escallier, Chen, Ben Abdallah, Inouye, Veselis, Grocott, Hudetz, Pryor, Pagel, Arya, Pong, Jacobsohn, Gyujeong, Kaiser, Downey, and Choi have critically revised the PODCAST protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the PODCAST trial.

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COMPETING INTERESTS

None of the authors have conflicts of interest to disclose.

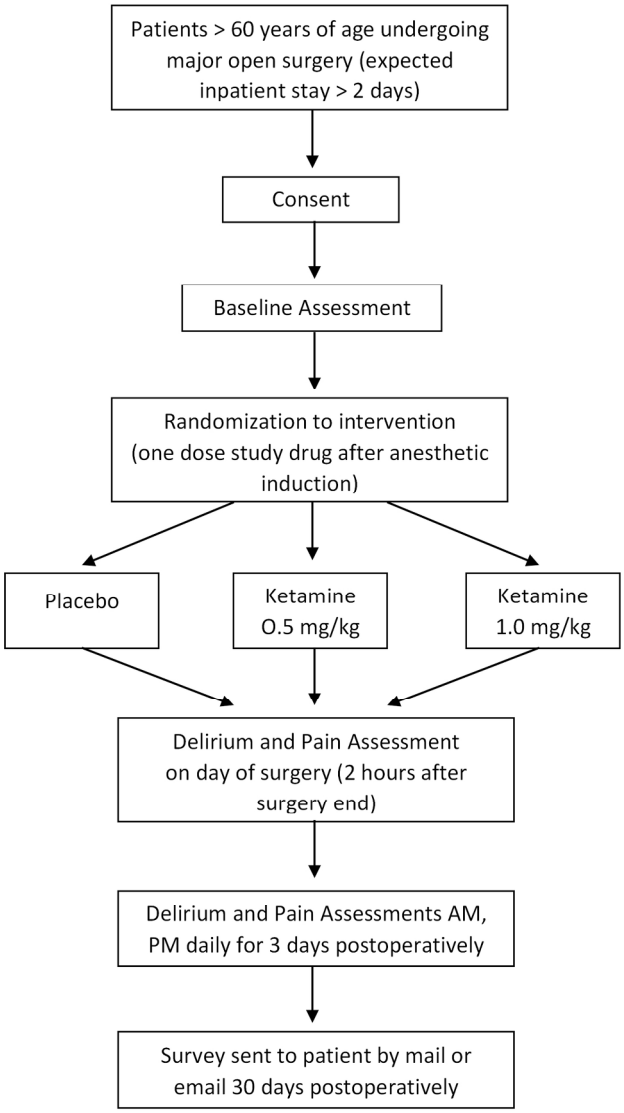

Figure 1: Study Enrollment
196x223mm (300 x 300 DPI)

Appendix A - Delirium and Pain Self-Assessment Questionnaire:

(Following the final delirium assessment, the following questionnaire will be given to patients):

A. Following your surgery, were there any periods that you felt you could not pay attention to people or things?

Yes No

B. If yes, can you say when:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

C. Following your surgery, were there any period that you felt you were not thinking in a logical or organized way?

D. If yes, can you say when:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

E. Did these feelings negatively affect your experience after the surgery?

Yes No

F. Following your surgery, were there any periods when your pain was uncontrolled?

Yes No

G. If yes, can you say when:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

H. Did any family members tell you that there were periods following your surgery that you felt you could not pay attention to people or things?

Yes No

I. Did any of your family members tell you that there were periods following your surgery when you were not thinking in a logical or organized way?

Yes No

J. Following your surgery, did you have bad dreams nightmares?

Yes No

K. If yes, can you say when:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

L. Following your surgery, did you have hallucinations (you saw things or heard things or felt things that were not there)?

Yes No

M. If yes, can you say when:

Today:

Today:	morning	afternoon
Yesterday:	morning	afternoon
Day before yesterday:	morning	afternoon

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1-3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	14
	6b	Explanation for choice of comparators	21
Objectives	7	Specific objectives or hypotheses	19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	21
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	30, 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	23
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	24
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	33
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	24
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	24-26
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	22

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	28
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	30
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	31
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	31
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	31
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	24-25
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	31
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	24-26
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	32
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	31
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	32
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	34
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	33
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	33
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	34
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	35
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	36
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	36
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	43
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	32
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	35
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	36
	31b	Authorship eligibility guidelines and any intended use of professional writers	36
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	36
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	separate file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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