Clinical Protocol

Efficacy of self-management of sedative therapy by ventilated ICU patients (L. Chlan and C. Weinert, MPIs)

Funding Sponsor: National Heart, Lung & Blood Institute, National Institutes of Health, 1 R01 HL130881-01

Study Products: Dexmedetomidine (Precedex)
The LifeCare® PCA Infusion System
The CADD Solis® infusion pump

IND Number: 111693 (E. Wittwer)

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Study Summary

Title	Efficacy of self-management of sedative therapy by ventilated ICU patients
Short Title	Patient-controlled sedation (PCS).
IND Number	111693
Phase	Phase II
Methodology	Study Design is an open label, randomized comparison of Patient self-management of sedative therapy compared to Usual Sedation Practice.
Study Duration	Estimated duration for the study is 5 years.
Study Center(s)	The study will involve three sites: University of Minnesota/Fairview Medical Center 500 Harvard Street, Minneapolis, MN 55455 Fairview Ridges Hospital 201 E. Nicollet Boulevard Burnsville, MN 55338 Fairview Southdale Hospital 6401 France Avenue South, Edina, MN 55435 Mayo Clinic 1216 2nd St, SW Rochester, MN 55902
Objectives	The primary objective of the study is to assess the efficacy of patient controlled sedation (Self-management of sedative therapy) using dexmedetomidine to reduce anxiety, delirium incidence and duration of mechanical ventilation compared to usual sedation practices in mechanically ventilated subjects.
Number of Subjects	N = 190; Mayo Clinic n=111; University of Minnesota Medical Center, Fairview Southdale Hospital, and Fairview Ridges Hospital n=79 subjects combined.
Diagnosis and Main Inclusion Criteria	Study subjects will be recruited from ICUs with intubated patients with respiratory failure who are able willing and able to operate the PCS push-button device and do not have conditions that could be worsened by dexmedetomidine (e.g., bradycardia, high degree heart block, or hypotension).
Study Product, Dose, Route, Regimen	Dexmedetomidine (Precedex®) Dexmedetomidine basal maintenance infusion rate of 0.2 to 0.7 mcg./kg/hr by the LifeCare® PCA Infusion System (Mayo Clinic) or the CADD Solis® infusion pump (University of Minnesota). Study patients may self-administer up to 3 mini-doses (0.25mcg/kg) per hour (every 20 minutes maximum with pump lock-out). The basal infusion rate will be titrated (up or down) every 2 hours based on the published algorithm [22].

Duration of administration	Up to 7 days of PCS. Subjects will be evaluated prior to hospital discharge for recall of ICU experiences, and again at 3- and 6-month post-ICU for recall of ICU experiences, functional status, well-being and quality of life

Reference therapy	Usual Sedation Practice (Nurse Administered)
Statistical Methodology	Duration of mechanical ventilation after enrollment, total sedative exposure and anxiety levels over time between groups will be assessed using linear mixed models and competing risk approach. Analysis of the CAM-ICU scores (delirium present/absent) over time between groups will be accomplished with mixed models using general estimating equations (GEE). Post-ICU outcomes will be analyzed with bivariate and limited multivariate analyses.

1. Introduction

This document is a protocol for a human research study. This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Each day approximately 55,000 patients are treated in U.S. adult ICUs [1]. Mechanical ventilation therapy is the major reason for ICU admission. While life-saving, intubation and mechanical ventilation cause unpleasant, distressful symptoms for patients such as anxiety, discomfort, fear, and dyspnea [2,3]. Numerous intravenous (IV) sedative and opioid medications are routinely administered by ICU nurses to ameliorate these symptoms and promote breathing synchrony with ventilators. While sedative therapy for ventilated ICU patients is a necessary, near-universal practice [4-7] the major issue is that patients are exposed to multiple, potent IV medications at high doses for prolonged periods leading to adverse outcomes such as prolonged ventilatory support and altered mental status. Since the 1970's researchers have tested new drugs; developed methods to measure the effects of sedation [8]; shortened the duration of mechanical ventilation by minimizing excessive drug exposure while maintaining patient comfort [9]; and documented the post-ICU effects of sedative exposure on mental health outcomes [10]. However, one belief underlying 30 years of ICU practice has never been challenged: the assumption that clinicians are the only ones who can judge sedation adequacy and make dose adjustments to achieve a subjective clinician-desired sedation goal. It is important to challenge this assumption because a large body of evidence shows that in both in-patient and out-patient surgery and diagnostic procedures, patients manage symptoms of anxiety and pain better than clinicians and are more satisfied with self-management of these symptoms as compared to clinician-managed [11-15].

Until recently, sedation practice was driven by the belief that ICU symptom management and enhancement of post-ICU psychological recovery required that patients receive enough medications to "sleep through" their severe illness. But research has demonstrated the deleterious effects of sedation

such as delayed time to spontaneous breathing trials, [16] an association between periods of blunted awareness and worse post-ICU psychological recovery [17] and an association of sedatives with delirium. [18] In fact, ventilated patients randomized to a light sedation regimen required one day less of ventilatory support and had *fewer* disturbing memories of the ICU compared to those patients given a deeper sedation regimen [19]. Furthermore, a recent trial showed that it was feasible to not sedate patients at all during mechanical ventilation (analgesics were given) and that non- sedation was associated with a shorter ICU stay [20]. Research has clearly demonstrated that sedative use can be tailored to specific patient symptoms and behaviors; many ventilated ICU patients can be awake or only lightly sedated if they are comfortable [21]. An analogous clinical scenario is management of post-operative pain for which pain and opioid requirements can vary substantially among patients. Rather than nurses administering "as needed" medications after responding to patient complaints or behaviors indicating pain, patient-controlled analgesia with IV pumps control pain better while requiring less medication [11-15] and is a preferred method of pain control by patients in the post-operative period which also decreases their anxiety [13].

1.2 Investigational Agents

Dexmedetomidine (Precedex®) is a selective alpha-2 adrenergic agonist with both sedative and analgesic properties. The pharmacokinetic profile has a rapid onset and short duration of action, producing light sedative properties. Dexmedetomidine has no active metabolites, does not diminish respiratory drive, and has minimal effects on cognitive function. Subjects receiving dexmedetomidine for sedation can be easily awakened without stopping the infusion. Precedex® was approved in 1999 (NDA 021038) for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, not to exceed 24 hours; or non-intubated patients prior to and/or during surgical and other procedures.

The LifeCare PCA® Infusion System with Hospira MedNet™ Software is an electromechanical infusion pump that uses a stepper motor that exerts pressure on an inserted drug vial to control the infusion of analgesic into a patient. The infuser is pole-mounted and includes an attached patient pendant that allows a patient to self-administer analgesia within physician- prescribed, programmed parameters that include delivery mode, PCA dose, lockout interval (5-120 min in 1 min increments) and/or 1 or 4 hour dose limits. The LifeCare PCA® Infusion System with Hospira MedNet™ Software is indicated for accurate, volumetric, infusion of analgesic drugs by continuous or patient-demanded (PCA) intravenous administration. The LifeCare PCA® Infusion System allows patients to self-administer drug within clinician programmed limits and/or hospital-defined medication limits. Safety features include the bar code reader that is designed to enhance patient safety and automate drug identification and concentration. The system allows the device to recognize pharmacy-generated bar codes and apply

hospital-defined medication limits. The LifeCare PCA® infusion pump is used in practice at the Mayo Clinic site. The CADD Solis® infusion pump is used in practice at the University of Minnesota site.

1.3 Clinical Data to Date

A review of short term (≤ 24 hour) patient controlled sedation by seventeen patients provided proof of principle that mechanically ventilated patients can use this technology [22]. While sedation level was appraised by the nurses as adequate, 70% of subjects received supplemental sedative and/or opiate medications. There were no self-extubations and 5 subjects experienced mild hemodynamic alterations known to be associated with the drug (persistent bradycardia or hypotension). Patient controlled sedation was discontinued for four subjects who developed hypotension. Patients rated dexmedetomidine for sedation favorably for self-management of anxiety and, relaxation level attained, and were comfortable in self-administration of a sedative agent. ICU nurses were generally satisfied with patient controlled sedation as a method for sedation, including satisfaction with dexmedetomidine as a sedative and with patients' responses to the drug.

In a small randomized trial pilot study conducted by Linda Chlan and Craig Weinert, MPIs (results submitted for publication), it was shown that intubated patients could be efficiently identified, consented, enrolled and treated with patient-controlled sedation using dexmedetomidine for up to 5 days. Hemodynamic effects were similar to that seen when dexmedetomidine is delivered by the usual nurse-managed method, there were no serious adverse events, daily anxiety assessments could be made and that patients rated the patient-controlled dexmedetomidine delivery method favorably. We did not find a shorter length of mechanical ventilation duration (although the study was not powered for that) or a reduction in anxiety compared to usual sedation method but there was an intriguing finding that no patient on PCS-dexmedetomidine developed delirium after enrollment whereas as 4 usual care patients did (p =.058, post-hoc analysis).

2. Study Objectives

2.1 Primary Objective:

The primary objective of the study is to assess the efficacy of patients' self-management of sedative therapy (SMST) using dexmedetomidine compared to usual sedation practices in mechanically ventilated subjects. Efficacy will be defined by statistically significant differences compared to usual sedation care comparator for:

a). Duration of mechanical ventilation after randomization
b). Incidence of delirium after randomization as assessed by the CAM-ICU tool.
c). Anxiety level over time after randomization.

2.2 Secondary Objectives:

Secondary objectives for the study include comparing PCS to a usual sedation comparator for the following variables:

a). Level of alertness over time after randomization as assessed by the

Richmond Agitation-Sedation Scale (RASS) scale.

b). Total sedative drug exposure after randomization assessed by two previously methods we have published—an aggregate sedative exposure (combining 9 possible sedative-analgesics) and a sedation dose frequency method [25].

c). Ventilator-free days defined as the number of days between successful weaning from mechanical ventilation and Day 28 after study enrollment.

2.3 Exploratory Aim:

The first exploratory aim is to compare post-ICU outcomes (physical/functional status, psychological well-being, and health-related quality of life) between MVPs randomized to SMST and those receiving nurse-administered sedative therapy. Statistically significant differences compared to usual sedation care comparator will be explored with the following:

a). Physical and Functional Status: Physical status will be assessed by the Katz Activities of Daily Living Scale (KADL), a widely used instrument that assesses basic physical abilities such as bathing, feeding, etc., with 6 questions.

b). Psychological Well-Being: We will use two instruments to measure psychological well-being. The first is the: (1) Patient Health Questionnaire (PHQ-9) a brief, 9-item tool that has been successfully administered via telephone to post-ICU patients, and the items closely track the cardinal symptoms of major depression. The second is the: (2) Posttraumatic Stress Disorder Checklist Event Specific (PCL) which will be used to measure symptoms of PTSD. The tool contains 17 event-specific items associated with PTSD; higher scores indicate PTSD.

c). Health-Related Quality of life: The Short Form-36 (SF-36) will be used to assess post-ICU quality of life. It contains 36 questions across 8 domains, with raw domain scores of 0-100; composite scores of "physical" and "mental health" can be compared to population norms.

The second exploratory aim is to compare immediate post-extubation recollections of ICU and to explore any relationship among cognitive experiences (CAM-ICU) and awareness (RASS scores) with mechanical ventilation complications (device disruption, self-extubation) and sedative exposure between MVPs randomized to SMST and those receiving nurse-administered sedative therapy. Statistically significant differences compared to usual sedation care comparator will be explored following 24-48 hours after extubation prior to discharge, and then again at 3- and 6-months after ICU discharge in accordance with the data collection points noted in exploratory aim #1:

a). The Intensive Care Experience (ICE) questionnaire will be used to assess patient recall, awareness of surroundings, satisfaction of care, and self- reported frightening cognitive experiences post-extubation prior to hospital discharge, and then again at 3- and 6-months. ICE questionnaire contains a total of 31 questions in four main categories: awareness of surroundings, frightening experiences, recall of experiences, and satisfaction with care. Previous investigations using the ICE questionnaire have administered 24-31 items, depending on the domains for assessment. We will administer 25 items at the three data collection time points.

3. Study Design

3.1 General Study Design

The study design will be an open label two-group randomized design with repeated measures and subjects randomly allocated to either: 1) Patient controlled, self-management of sedative therapy using dexmedetomidine or 2) nurse-administered sedative therapy (usual care). The protocol will last up to seven days or until the patient exits the study. After 7 days the sedative regimen reverts to usual care with drug choice by the attending consultant physician. We will obtain from all participants who are alive and living in their own homes data on post-ICU physical and functional status, psychological well-being, and health-related quality of life. These assessments will be obtained over the telephone at 3- and 6-months post-ICU discharge. A member of the research team will contact the individual at the designated time period and ascertain a convenient time to obtain the data. We will request a home phone number for this follow-up prior to hospital discharge or obtain it from the electronic health record.

3.2 Primary Study Endpoints

a) Duration of mechanical ventilation after randomization
b) Incidence of delirium for up to 7 days after randomization
c) Anxiety level over time by the visual analog scale (VAS-A) measure for up to 7 days

3.3 Secondary Study Endpoints

The secondary endpoints to be analyzed in this study include

a) Level of alertness of subjects after randomization and for up to 7 days
b) Total sedative exposure for up to 7 days after randomization
c) Ventilator-free days after randomization

4. Subject Selection and Withdrawal

4.1 Inclusion Criteria

Subjects may be included in the study if all of the following conditions exist:

1. Subject is acutely mechanically ventilated during the current hospitalization

2. Subject is currently receiving a continuous intravenous infusion of a sedative/opioid medication(s) or has received at least one intravenous bolus dose of a sedative/opioid medication in the previous 24 hours (fentanyl, hydromorphone, ketamine, morphine, midazolam, diazepam,

lorazepam, propofol, haloperidol, dexmedetomidine).

3. Subject must pass pre-PCS screening test (see below **4.4**) and be assessed RASS -2 to +1
4. Subject Age ≥ 18 years
5. Subject or their proxy is capable of providing informed consent

4.2 Exclusion Criteria

Subjects will be excluded from the study if any of the following conditions exist:

1. Aggressive ventilatory support or prone ventilation.
2. Hypotension (systolic blood pressure < 85 mmHg) requiring a vasopressor at a dose greater than norepinephrine or epinephrine 0.15 mcg/kg/min or vasopressin > 2.4 units per hour. Subjects will be excluded if they require more than one continuous infusion of a catecholamine vasopressor medication simultaneously. Subjects will be excluded if the vasopressor dose was higher than norepinephrine or epinephrine 0.15 mcg/kg/min, vasopressin > 2.4 units per hour, phenylephrine >3 mcg/kg/min, dopamine >10 mcg/kg/min or dobutamine at any dose in the prior 6 hours. If dopamine is being used to increase heart rate, rather than as a vasopressor for hypotension, subject will be excluded.
3. Second or third degree heart block or bradycardia (heart rate < 50 beats/min).
4. Paralysis or other condition preventing the use of push button device
5. Positive pregnancy test or lactation
6. Acute hepatitis or acute liver failure (direct bilirubin >5 mg/dL)
7. Acute stroke or uncontrolled seizures.
8. Acute myocardial infarction within 48 hours prior to enrollment.
9. Severe cognition or communication problems (such as coma, deafness without signing literacy, physician-documented dementia)
10. Assessed RASS -3, -4, -5 or RASS +2, +3, +4
11. Chronic ventilator support in place of residence prior to current hospitalization.
12. Imminent extubation from mechanical ventilator support.

4.3 Study Exit Criteria

Subjects will exit from the study if any of the following conditions exist:

1. Subject completes protocol
2. Subject (or proxy giving initial consent) voluntarily withdraws from the study
3. Subject death
4. Subject is extubated and remains free of invasive ventilation for 24 hours
5. Subject transfers from the ICU

6. Subject experiences a serious persistent adverse event such as unexplained rash or sustained hemodynamic instability as defined in the SEDCOM [23] trial (e.g., systolic blood pressure < 80 or > 180 mmHg, diastolic < 50 or > 100mmHg despite the use of a vasopressor at dose greater than norepinephrine or epinephrine 0.15 mcg/kg/min, vasopressin > 2.4 units per hour, phenylephrine >3 mcg/kg/min, dopamine >10 mcg/kg/min, dobutamine at any dose, or two catecholamine vasopressors at any dose, or heart rate < 40 or > 120 beats/min)
7. Pregnancy

4.4 Subject Recruitment and Screening

Subjects will be recruited from three facilities located 90 miles apart. Research staff will ask attending physician consultants each screening day about approaching potential study eligible patients. Inclusion and exclusion criteria will be reviewed; only those patients approved for the study by the primary medical care team will be approached for potential study participation.

The University of Minnesota Medical Center (UMMC) Fairview, Medical and Surgical ICUs in Minneapolis, MN. UMMC is the primary teaching hospital of the University of Minnesota Medical School. Combined, these adjacent ICUs have 47 staffed beds; admit about 1500 patients annually of which approximately 900 require mechanical ventilation.

Fairview Southdale Hospital has a single mixed med-surgery/Neuro/CV surgery ICU with 22 bed capacity with approximately 720 ventilated patients annually. Their physician/NP intensivist providers are drawn from the same ICU program as UMMC thereby ensuring that the general ICU practice regarding sedation and mechanical ventilation is similar to that of UMMC. Southdale uses the same PCS drug delivery machines as UMMC and the drug will be dispensed by the Fairview Investigational Drug Service in the same manner as UMMC.

Fairview Ridges Hospital has a medical-surgical ICU with 12 beds. Their physician intensivist providers are drawn from the same ICU program as UMMC thereby ensuring that the general ICU practice regarding sedation and mechanical ventilation is similar to that of UMMC. Ridges uses the same PCS drug delivery machines as UMMC and the drug will be dispensed by the Fairview Investigational Drug Service in the same manner as UMMC.

St Mary's Campus is the main hospital for patients at the Mayo Clinic Hospital-Rochester and has 80 adult ICU beds. The Methodist Campus has 21 adult ICU beds. The MICUs (24 total beds) average 2900 patient admissions per year with approximately 880 mechanically ventilated patients/year from which to enroll participants.

Our previous experience with recruiting mechanically ventilated subjects for PCS studies shows a 45% consent yield rate, which should easily permit enrolling 190 patients over the study period —111 at Mayo Clinic and 79 at UMMC.

The three facilities utilize electronic medical records systems, physician-order entry and have Research Investigational Drug Pharmacies that can dispense and monitor study medications. The Mayo Clinic site uses the Hospira LifeCare® pump in routine clinical use so RN staff will be familiar with it when used in study patients. The University of

Minnesota sites use the CADD Solis® infusion pump. RN staff at the University of Minnesota sites are familiar with the infusion pump operations.

Informed Consent will be obtained from either the patient or via proxy consent of the patient's legally authorized representative (LAR).

Subjects will be screened for participation with a pre-PCS screening test to evaluate motor abilities, alertness, and presence of delirium (Uploaded to Section 47, Supporting Documents). Motor abilities and alertness level will be evaluated by a trained research staff that will consist of the following: Motor ability will be assessed by placing the medication push-button activation device button in the patient's hand and asking them to depress the button or click a ball-point pen. An audible tone is emitted after the device is engaged, which will verify the patient has enough strength to depress the button. The alertness screen will consist of the trained research staff assessing the subject's ability to communicate and appropriately follow commands, including direction to depress the actual PCS button and following verbal instructions accurately to do so. The two-step process of the Confusion Assessment Method-ICU (CAM-ICU uploaded to Section 47, Supporting Documents) will also be administered to determine a patient's alertness and for the presence of delirium. Step one of the assessment process consists of arousal and alertness assessment using the Richmond Agitation-Sedation Scale (RASS). **Any patient will need to be assessed as RASS level of -2 to +1 (-1 indicates drowsy, easily arousable and wakens with eye-opening/eye contact to voice; -2 indicates light sedation awakens with eye contact to voice) to be eligible for study participation**. Step two of the assessment process includes administration of the Confusion Assessment Method for the ICU (CAM-ICU) which consists of the delirium assessment component. The dichotomous result is either delirium absent (CAM-ICU negative) or delirium present (CAM-ICU positive). Potential participants **must** be RASS -1 to +1 **AND** CAM-ICU negative to provide their own informed consent.

Procedures for Proxy Consent

If a potential participant passes the pre-screening test, is RASS -2 to +1 ***except*** is found to be CAM-ICU positive (delirium present), proxy consent must be pursued as detailed. Presence of delirium will not automatically exclude any potential participants. Given delirium is a transient syndrome, if a patient can follow commands, rate his/her anxiety, and follow commands to independently depress the PCS push-button device, she/he will be considered for enrollment by proxy after the research personnel discusses the pre-screening results with the attending consultant physician and Dr. Gajic (or his designate) at Mayo Clinic or Dr. Weinert (or his designate) at UMMC, Fairview Southdale, and Fairview Ridges.

We estimate that some patients who are otherwise eligible (RASS -2 to +1), pass the pre-screening test but are CAM-ICU+ (delirium present) will not be able to provide their own informed consent. In this case, we will use proxy consent for any patient who is willing and able to self-medicate with dexmedetomidine by verbal assent with an affirmative head nod "yes". We are an experienced research team that is familiar with the sometimes limited capacities of mechanically ventilated patients and the need for obtaining proxy consent, such as patients too fatigued or weak to actively participate in a lengthy consent process, decreased ability to maintained focused concentration, or may be more heavily sedated for a short duration such as for a bedside procedure.

We will obtain consent for participation from a family member or legally authorized

representative (LAR) if an eligible patient is unable to participate in a lengthy consent process and/or CAM-ICU+ yet is deemed to be a promising candidate for the protocol. Patients must be reasonably alert (RASS -2 to +1), follow commands appropriately and consistently, and be able to depress the push- button activation device to be considered for study participation with consent via proxy. A member of the research team will approach the designated proxy LAR and explain the study and what is being asked of the proxy if consent is provided to participate in the study. Each proxy will then read the consent form and be asked to re-phrase to a member of the research team what the study aims are, how long the patient will remain in the study, and if payment will be received. Opportunity will be provided for asking questions concerning the protocol. If the LAR is not available at the bedside, and not expected to be for the rest of the day, study personnel will contact him/her by telephone and explain the study and what is being asked of the LAR if consent is provided to participate in the study. A DocuSign email will be sent to the LAR with a link to the consent form. The consent form will be reviewed with the LAR. The LAR will be asked to rephrase to the study team member what the study aims are, how long the patient will remain in the study, and if payment will be received. If the LAR agrees to provide consent verbally, the study team member will direct the LAR to electronically sign the consent form.

Females less than 50 years old and who are of unknown fertility (pregnancy) status after review of the medical record including documentation of surgical procedure or medical condition that would make pregnancy unlikely and/or recent serum or urine pregnancy test, have to consent to a urine or serum pregnancy test to be performed in the hospital lab at no cost to the patient. If the test is positive, the patient and her doctor will be informed and the subject then will be withdrawn from the study BEFORE randomization.

If the female is > 50 years old or has clear documentation of a surgical procedure or medical condition that would make pregnancy unlikely or has a recent serum or urine pregnancy test that is negative, then they can proceed to randomization.

4.5 Subject Randomization

Subjects (n =228 total accounting for 20% attrition to attain a target sample of n = 190) will be assigned to either the Usual Sedation Practice or Patient Controlled Sedation arms of the study based on a block randomization plan developed by the Mayo Clinic study statistician and administered by the Research Pharmacy Investigational Drug Service at both hospitals. For patients randomized to the experimental arm, dexmedetomidine will be prepared and dispensed with Research Pharmacy prepared, bar-coded medication cartridges. Randomization will occur after written consent is received.

4.6 Early Withdrawal of Subjects

Subjects will be withdrawn if any of the Exit Criteria listed in Section 4.3 are present. If subjects are withdrawn prior to extubation, they will be transitioned to usual sedation practice per the primary medical care team. For any subject who completes the 7-day PCS protocol and is still receiving mechanical ventilatory support, Dr. Weinert at UMMC or Dr. Gajic at Mayo
(or their designates) will consult with the subject's attending physician for the transition to primary care team sedation management. All data will be considered for analysis regardless of length of time on protocol.

5. Study Drug

5.1 Description

Dexmedetomidine (Precedex®) is a selective alpha-2 adrenergic agonist with both sedative and analgesic properties. The pharmacokinetic profile has a rapid onset and short duration of action, producing light sedative properties. Dexmedetomidine has no active metabolites, does not diminish respiratory drive, and has minimal effects on cognitive function.

5.2 Treatment Regimen

We will use a continuous basal infusion (0.2-0.7 mcg/kg/hr) with 3 allowable patient-controlled self-boluses per hour (0.25 mcg/kg) each with a 20-minute lock-out. The Lifecare PCA® Infusion System is the infusion pump used at Mayo Clinic and the CADD Solis® infusion pump is used at the University of Minnesota sites; infusion pumps will be set up by the patient care nurse. The pump will be utilized in the PCA + continuous mode. Intermittent doses are delivered in 1 ml over 35 seconds. Delivery accuracy is ± 5% for continuous delivery rates > 1 ml/hour. Settings, dose delivery times and aggregate dosing are recorded by the pump for later retrieval.

5.3 Preparation and Administration of Study Drug

Dexmedetomidine will be stored, prepared and dispensed from the Central Pharmacy at Mayo Clinic and from the Investigational Drug Service Pharmacy at UMMC, Fairview Southdale, and Fairview Ridges. When study drug is requested for a subject, the respective pharmacy will obtain the study dexmedetomidine and complete the required paperwork documenting the lot number and vials utilized for the specific study subject.

For patients weighing between 50 and 164 kg at the time of study enrollment, under strict aseptic technique, 720 µg/7.2 ml will be added to 52.8 ml of 0.9% sodium chloride; this will yield a concentration of 720 µg/60 ml (or 12 µg/ml). Two 30 ml syringes will be drawn up from the bag each containing 360 µg/30 ml of dexmedetomidine. Dexmedetomidine will be delivered via a pharmacy-prepared bar-coded cartridge syringe manufactured for use with the LifeCare PCA® infusion device as described above. Preparation date and time will be recorded. Within 48 hours of initial preparation, the volume of the remaining preparation will be recorded and a fresh drug preparation will be supplied for the subject.

For patients weighing between 165 and 260 kg at the time of enrollment, under strict aseptic technique, 1200 µg/12 ml will be added to 48 ml of 0.9% sodium chloride; this will yield a concentration of 1200 µg/ 60 ml (or 20 µg/ml). Two 30 ml syringes will be drawn up from the bag each containing 600 µg/30 ml of dexmedetomidine. Each syringe will be clearly labeled “FOR > 165 kg patients ONLY.” Dexmedetomidine will be delivered via a pharmacy-prepared bar-coded syringe manufactured for use with the LifeCare PCA® infusion device as described above. Preparation date and time will be recorded. Within 48 hours of initial preparation, the volume of the remaining preparation will be recorded and a fresh drug preparation will be supplied for the subject.

6. Study Procedures

Usual Care: Subjects will receive standard care for the respective ICU which consists of nurse-administered sedative therapy as ordered by the primary care team.

Anxiety and mental status/alertness assessments will be performed by a member of the research team three times each day, up to 7 days or until the ICU phase of the protocol is completed (i.e., extubation, transfer out of ICU, patient withdraws or is withdrawn from study), for subjects in both groups.

Self-management of Sedative Therapy (SMST) with Dexmedetomidine PCS Protocol: The PCS dosing algorithm will consist of a continuous basal infusion (0.2-0.7 mcg/kg/hr) with 3 allowable patient-controlled self-boluses per hour (0.25 mcg/kg) each with a 20-minute lock-out. Dr. Weinert or his designate at UMMC, Fairview Southdale, and Fairview Ridges or Dr. Gajic or his designate at Mayo Clinic will write the PCS medication orders; each study patient on dexmedetomidine will begin the study with a continuous, basal infusion of 0.2 mcg/kg/hr; set up by the patient care nurse. Patient-care nurses will increase or decrease the basal infusion rate based on the number of mini-bolus doses self-administered from the subject in the prior two hours. Subjects can receive bolus supplemental sedative medications (benzodiazepines and/or opioids) as ordered by Dr. Weinert or Dr. Gajic (or their designate) if needed in the judgment of the patient-care nurse. Subjects will be monitored closely by research personnel during the first 4 hours on protocol. Every 4-hour heart rate and blood pressure recordings will be abstracted from the medical record daily during each subject assessment visit. Alert adverse events will be reported by research personnel or the patient-care nurse to first the attending physician and then to the safety monitor.

Nurse alert parameters to notify the attending physician consultant and study physicians (Drs. Gajic, Weinert or their designate) include: heart rate (HR) < 55 beats per min for > 5 min; systolic BP < 90 mm Hg; diastolic BP < 55 mm Hg; or mean arterial pressure < 60 mm Hg on two measurements 10 min apart.; persistent inability to understand rationale for triggering the PCS device despite education and demonstration; or marked worsening of respiratory status requiring aggressive ventilatory support with deep sedation and/or chemical paralysis.

Data Collection Measures and Procedures

Study entry demographic and descriptive data: Data to be recorded includes: age, gender, race, ethnicity, admission and enrollment weight, medical diagnoses, indication for ventilatory support, medications including sedative medications in the prior 24 hours, ventilator settings, and severity of illness measured by APACHE III score. The APACHE III is used to stratify patients during the first 24 hours of ICU admission to determine severity of illness and predict mortality; a higher score is associated with an increased risk of death. Data to determine illness severity will be abstracted by a member of the research team from the medical record. For daily illness severity, Sequential Organ Failure Assessment (SOFA) will be scored each day from the medical record for the length of study enrollment. In order to describe this sample of ICU patients, data to calculate the length of ICU stay as well as length of mechanical ventilation will be collected. Any differences in illness severity, SOFA scores, age, or sex will be considered as covariates in subsequent analyses.

Daily Measures on Protocol.

Sedative exposure. *For all subjects*, we will measure exposure to 9 commonly administered intravenous sedative and analgesic medications (lorazepam, midazolam,

propofol, morphine, hydromorphone, fentanyl, dexmedetomidine, haloperidol, ketamine) for up to 7 days after enrollment (primary drug endpoint for analysis). We have developed a method (the sedation intensity score) [25] to aggregate dose frequency and dosing of intravenous medications from disparate drug classes by day. The 9 possible intravenous drugs tracked are summarized individually over all subjects and time periods to obtain estimates of their medians and quartiles. Each drug during each 4-hr period is then assigned a ranking as follows: 0 for drug not used, 1 for the bottom quartile, 2 for the second quartile, 3 for the third and 4 for the fourth. These scores are then summed for the day over the six 4-hour blocks to produce a daily sedation intensity score. Our analysis will compare the mean sedation intensity scores between the PCS and usual care group. For the PCS group, the patient care nurse will record every two hours the basal infusion rate, number of patient triggers, and actual doses delivered.

We will also use *a dose-frequency analysis* based on recent trials that suggest the mechanism by which sedation protocols result in more rapid weaning from ventilatory support is by reducing the time exposure to sedatives [9,26]. We will divide a 24-hr day into six, 4-hour time blocks and, for each of the 9 intravenous drugs, sum the occurrences in which a non-PCS drug was administered at least once during that interval. The amount of drug, count of doses above one, and type of administration (bolus vs. infusion) are not influential in this approach.

Alertness and Delirium. Level of arousal will be assessed three times each day (07:00, 13:00, 19:00; +/- 2 hours) by research study staff with the Richmond Agitation- Sedation Scale (RASS). The RASS is based on a 10-point scale, with four levels of agitation ranging from +1 (*restless*) to +4 (*combative*), one level representing an alert and calm state (0), and five levels of sedation ranging from -5 (*unarousable*) to -1 (*drowsy*). These assessments will be completed by a member of the research team ((investigator, study coordinator or member of the CRTU (Mayo Clinic only)) at 07:00,13:00, and 1900 (+/- 2hours). The RASS scores obtained at 07:00, 13:00 and 19:00 (+/- 2 hours) will be compared between groups and correlated with sedative exposure and dosing by drug class (benzodiazepine midazolam equivalents, morphine equivalents for opioids, propofol, and dexmedetomidine) to address our secondary aim.

The Confusion Assessment Method-ICU (CAM-ICU) [24] will be used as a pre-enrollment delirium screening tool and to measure level of alertness and presence of delirium three times each day in both groups. The pre-enrollment delirium screening will be obtained by a member of the research team (investigator or study coordinator). These assessments will be completed by a member of the research team (investigator, study coordinator or member of the CRTU (Mayo Clinic only)) at 07:00, 13:00, and 1900 (+/- 2 hours). Any positive delirium findings will be reported by the research staff to the primary care team. Research personnel will be trained by Dr. Tracy at UMMC and Dr. Chlan at Mayo Clinic in assessment with the CAM-ICU using free web resources (www.icudelirium.org).

Anxiety rating. Anxiety, defined as a state marked by apprehension, agitation, increased motor activity, arousal, and fearful withdrawal [27] will be obtained from subjects by a member of the research team (investigator, study coordinator, or member of CRTU (Mayo Clinic only)) prior to randomization and at 07:00,13:00, and 1900 (+/- 2 hours). This will be the primary symptom endpoint for analysis. Subjects will be asked three times daily to rate their current level of anxiety on the visual analog scale-anxiety (VAS-A) in response to, “How are you feeling right now?” A 100-millimeter vertical line will

be anchored on each end by statements ‘not anxious at all’ to ‘the most anxious I have ever been’. The VAS-A will have a vertical orientation, as it is more sensitive and easier for subjects to use, particularly for those with a narrowed visual field or when under stress [28,29]. Subjects will be asked to mark their current anxiety level on the vertical line. Scores will be derived by the distance in millimeters from the bottom anchor to the mark placed by the subject, yielding interval level data [30,31]. Reason(s) for not obtaining any of the anxiety assessments will be recorded by the research staff.

Duration of mechanical ventilatory support. This will be calculated from the time of study enrollment to clinician-ordered extubation, withdrawal of ventilatory support or death for the incident ICU admission. Patients will be required to remain free from mechanical ventilatory support for 24 hours to be considered liberated from mechanical ventilation. Unplanned self-extubations and re-intubations and timing and frequency of tracheostomy will be recorded.

Mechanical Ventilator-Related Outcomes. We will obtain data on the following important mechanical ventilator-related outcomes. These data will be used to describe the clinical course for all study participants: tracheostomy placement, reintubation rates, time to first and successive weaning trials (initiation of pressure support or t-piece weaning), extubation, ICU discharge destination (step-down, long-term acute care hospital, rehabilitation or skilled nursing facility, death), ICU or hospital readmission at any time from transfer/discharge during the 6-month follow-up period.

Protocol adherence. A checklist will be completed daily by the research staff to monitor the number of days subjects are able to use the PCS device for up to 7 days. A checklist will also be used to monitor the ability of the ICU nurses to adjust and adhere to the PCS infusion protocol per instructions.

Daily adverse event monitoring. A member of the research team will record and report the presence of hypotension, bradycardia (known adverse effects of dexmedetomidine), delirium, self- extubations, and protocol deviations related to drug, pump or both. Heart rate and blood pressure will be abstracted from the medical record. Research staff or ICU nurses caring for PCS subjects will alert the attending physician and the safety monitor for sustained (lasting > 30 min.) systolic blood pressure < 80 or > 180 mmHg, diastolic < 50 or > 100 mmHg; heart rate < 40 or > 120 beats/min for any necessary intervention or protocol withdrawal.

Post-PCS Satisfaction Survey. Upon completion of the SMST PCS protocol, we will query subjects about their satisfaction with self-administration of medication to manage anxiety, ease of medication administration, and the resulting level of relaxation.

Post-Extubation ICU Recall Prior to Hospital Discharge and at 3 and 6 months
The Intensive Care Experience (ICE) questionnaire will be administered to all subjects 24-48 hours after extubation and prior to hospital discharge or transfer out of ICU, and then again at 3 and 6 months after ICU discharge in accordance with the Post-ICU Outcomes data collection points noted below. The ICE questionnaire contains 31 total questions in four main categories: awareness of surroundings, frightening experiences, recall of experiences, and satisfaction with care. We will administer 25 questions to subjects at the three assessment time points. Subjects who are not extubated prior to ICU transfer or hospital discharge will not be assessed for ICU recall with the ICE questionnaire.

Post-ICU Outcomes at 3- and 6-months

Telephone follow-up will be completed at 3 and 6 months after date of study randomization.

Physical and Functional Status: Physical status will be assessed by the Katz Activities of Daily Living Scale (KADL), a widely used instrument that assesses basic physical abilities such as bathing, feeding, etc., with 6 questions. The Functional Activities Questionnaire (FAQ) contains 10 questions that assess instrumental activities of daily living that require higher-order abilities, such as cooking, driving, managing finances, medications, etc.

Psychological Well-Being: We will use two instruments to measure psychological well-being. The first is the: (1) Patient Health Questionnaire (PHQ-9) a brief, 9-item tool that has been successfully administered via telephone to post-ICU patients, and the items closely track the cardinal symptoms of major depression. The second is the: (2) Posttraumatic Stress Disorder Checklist Event Specific (PCL) which will be used to measure symptoms of PTSD.

Health-Related Quality of life: The Short Form-36 (SF-36) will be used to assess post-ICU quality of life. It contains 36 questions across 8 domains, with raw domain scores of 0-100; composite scores of "physical" and "mental health" can be compared to population norms.

7. Statistical Plan

Estimates of Effect Sizes, Sample Size, and Statistical Power. Our primary outcomes are anxiety, duration of mechanical ventilation, and delirium. In our previous study, overall, anxiety decreased over time for the PCS group by 5 points from 58.1 to 53.1 (0-100 visual analog scale), whereas it increased by 15.5 points from 43.7 to 53.9 for the UC group. The delta change for anxiety = .45 for an effect size = .11 with a sample size of 95 per group (190 total). We base our target sample size on these anxiety data for our efficacy RCT. During the study, no patients randomized to DEX-PCS became delirious, while four patients randomized to UC group developed delirium. Because of small numbers, the *p* value was .058. A sample of 35 subjects per group would be required (70 total). The power calculation for duration of mechanical ventilatory support after study enrollment (Mann-Whitney U) with an effect size of .41 would = 43 per group (86 total).

Using *Optimal Design* software, we estimated the power for multilevel models approximating our study design. A sample size of 95 patients per arm, 190 total (at a minimum 7 data collection points for each, resulting in ~1,050 observations) will have greater than 80% power to detect small to moderate effects (i.e., 0.11 or greater) in between-group differences in anxiety, delirium, and duration of mechanical ventilation at alpha = .05 for all proposed models.

Preliminary Analyses. In initial analyses, we will screen to identify and, if necessary, correct outliers, data entry errors, or other logical inconsistencies. After data cleaning, we will calculate descriptive statistics to ensure the quality of the data (check distributions, examine outliers) and describe the sample. Where necessary, we will consider variable collapsing or power transformations. We will evaluate the psychometric qualities (reliability, convergent and discriminant validity) of the scales, employing both exploratory

factor analyses and SEM measurement models. We will identify potential effects of respondent attrition. The bivariate analyses will include independent and dependent *t* tests, correlations, one-way ANOVAs, and repeated measures ANOVAs. Analyses will include both Intention-to-treat and per-protocol.

Analysis by Aims. Our **primary aim** is to determine the efficacy of PCS compared to nurse-administered sedative therapy on **anxiety, duration of mechanical ventilation after enrollment,** and **presence of delirium** in ventilated patients. All three outcomes will be assessed with multilevel models. We will conduct multilevel growth curve analyses, to model the trajectories of anxiety as predicted by group in 190 patients, while controlling for illness severity, age, sex, or sedative exposure. The level 1 sub-model will estimate how each patient's stress changes over one week. The level 2 sub-model will relate the inter-individual differences to intervention group and other time-invariant predictors (such as biological sex) and will estimate a subject's initial anxiety level and rate of change in anxiety over the week. Anxiety will be modeled in terms of random subject effects (intercept and time trends) to account for individual differences in how patients change over time. We will begin with a linear model for time but will investigate nonlinear effects as suggested by the data. Subsequent models will contain time-varying covariates (i.e., sedative exposure and acuity (APACHE III)) and thus will be able to focus on within-subjects effects, that is, whether within-subject differences in the covariates are associated with within-subject differences in anxiety. The most appropriate covariance structure for the residuals will be determined after data collection and the correlation of responses over time is estimated. Several covariance structures will be examined and the resulting models compared for fit using the quasi-likelihood independence model information criterion (QIC).

Statistical analysis for the duration of mechanical ventilation outcome will be time (days) from study enrollment to first ventilation free day (24 hours free of mechanical ventilation support after extubation) as an outcome will be performed using competing risk approach as referenced in Fine and Gray (1999). In this analysis, death will be considered as a competing event. When delirium is operationalized as a dichotomy (present vs. absent) over time we will fit the models using general estimating equations (GEE). For binomial data, the most appropriate link function is the logit (logistic regression model) and, for incidence, the log (Poisson regression in Log-Linear Model).

Withdrawal of mechanical ventilatory support is not considered equivalent to death but the same as a medically planned extubation (i.e., patient who is determined to be 'ready' for extubation by the medical care team). For those enrolled patients who undergo terminal withdrawal of ventilatory support, we will ascertain their vital status up to 30 days after enrollment in the study ended.

Our first **secondary aim** is to: (1) Examine level of **alertness (RASS)** and **sedative exposure** (frequency and intensity) in patients randomized to SMST compared to those patients receiving nurse-administered sedative therapy. We hypothesize that SMST patients will be more alert and be exposed to less sedation than those who receive nurse-administered sedative therapy. After bivariate tests, such as repeated measures ANOVAs, we will fit multilevel models as described in our primary aim. Similar analyses will be used for the exploratory aim data.

Our second **secondary aim** is to: (2) compare ventilator-free days in patients randomized to SMST to those patients receiving nurse-administered sedative therapy. Ventilator-free

days are defined as the number of days between successful weaning from mechanical ventilation and day 28 after study enrollment. A score of zero will be assigned to any patient who dies within 28 days or remains on the ventilator for 28 days or more. For other patients that are alive and successfully weaned from mechanical ventilation, a score of 28 minus number of days on ventilation will be assigned. Ventilator-free days will be analyzed using Wilcoxon rank sum test.

Our first **exploratory aim** is to compare post-ICU outcomes (physical/functional and psychological well-being; health-related quality of life) between patients randomized to SMST and those receiving nurse-administered sedative therapy. We anticipate conducting bivariate and limited multivariate analyses for these data.

Our second exploratory aim is to compare immediate post-extubation recollections of ICU and to explore any relationships among cognitive experiences (CAM-ICU) and awareness (RASS scores) with mechanical ventilation complications (device disruption, self-extubation) and sedative exposure between MVPs randomized to SMST and those receiving nurse-administered sedative therapy. Statistical comparisons between the two study groups will be carried out for total scores on the 25-item ICE questionnaire as a whole, as well as and its 4 main categories, will be performed using two sample t-test or Wilcoxon rank sum test as appropriate. In an event there are baseline imbalances between the two groups, we will use linear regression approach to adjust for those variables with imbalances. Analysis will be performed separately for each of the three time points (24- 48 hours, 3 months, 6 months).

8. Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs a hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious

outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 24 hours following extubation, study withdrawal, transfer out of ICU or 24 hours after completing 7 days on protocol from the time of randomization. ***Refer to Data and Safety Monitoring Plan (DSMP) for additional details.***

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events. Refer to the Data Safety Monitoring Plan and the Data and Safety Monitoring Board charter.

8.4 Stopping Rules

Initial protocol suspension rules are as follows for an individual subject's participation in the study:

- Persistent (>30 min.) adverse hemodynamic effects as in the SEDCOM [23] trial including systolic blood pressure < 80 or > 180 mmHg, diastolic blood pressure < 50 or > 100 mmHg; heart rate < 40 or > 120 beats/min.;
- Persistent inability to understand rationale for triggering the PCS device despite education and demonstration; or
- Marked worsening of respiratory status requiring aggressive ventilatory support with deep sedation and/or chemical paralysis.

Any subject who experiences any of the above will first be evaluated by the attending physician consultant (or his/her designate). He/she will communicate their findings to Dr. Weinert at UMMC or Dr. Gajic at Mayo Clinic (or their designate) and their opinion of any event(s) regarding the suitability of an

individual subjects to continue on the study protocol. Dr. Weinert or Dr. Gajic (or their designate) will review the circumstances and will decide whether to restart the protocol or withdraw the subject from the protocol.

The study does not have any pre-planned interim analysis. Our study team will monitor adverse and serious adverse events on a monthly basis. If there is clinically meaningful imbalance in such event related to the experimental intervention irrespective of statistical significance, DSMB members will be notified. Decision of continuation versus stopping the study will be made in consultation with DSMB members.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigators to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety- monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. In addition, a blinded adverse event attribution adjudication committee comprised of clinicians independent of the research team is in place at each site. It is the responsibility of the adjudication committee to judge the relatedness of any adverse events (AE) or serious adverse events (SAE) relatedness to the study protocol, and then report back to the responsible PI or their designate. If any AE or SAEs occur, the respective site principal investigator (or her/his designate) will alert the committee members to the need for review and assignment of relatedness/not related to the protocol.

8.6 Independent Data and Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established for this study by the Midwest Area Research Consortium for Health (MARCH) which is comprised of Midwest CTSA institutions, inclusive of the Mayo Clinic, University of Minnesota and Fairview Southdale. The Board will consist of a minimum of 5 individuals, including a statistician, mental health professional and expertise in critical care and pharmacology. All members will be independent of the study and the research team members from the University of Minnesota, Fairview Southdale, Fairview Ridges and the Mayo Clinic.

The Board will be asked to:

- Meet in face-to-face or conference call meetings at a frequency to be determined by the DSMB, based on the accrual rate, data complexity, and frequency of adverse events.
- Review all Serious Adverse Events (SAEs) pursuant to immediate notification by the Principal Investigator. Data and information will be provided by study staff.
- Review summaries of selected cases and review study data.
- Recommend changes in the protocol that are consistent with their findings concerning safety and or clinical practice.

- Issue a written summary of finding and recommendations for each meeting.

Potential Risks to Human Subjects
Physiological Risks
There are several potential risks associated with participation in this study for subjects randomized to the SMST group. Known side-effects of dexmedetomidine include hypotension and bradycardia, which will be included in the study consent form. We anticipate that this will occur in 10% of subjects.

Another risk is that SMST subjects may not be able to self-administer the study medication, possibly due to confusion about using the push button device or, less likely, because of severe weakness. This might result in inadequate control of symptoms. Similarly, a SMST subject might activate the device appropriately but remain subjectively anxious. In both situations, our study protocol minimizes these risks by permitting supplemental medications to be administered by the subject's bedside nurse. Based on our prior work, we estimate that supplemental sedatives will be administered at least once during the 7 day study interval to > 50% of SMST subjects. Because this intervention can be given quickly, we estimate that the subject's risk of experiencing uncontrolled anxiety or other significant symptoms is very low (< 5%).

Based on prior work, we estimate that unselected patients requiring more than 48 hours of mechanical ventilation have a 2 month mortality of 30%, most of that occurring within the first three weeks. Our entry criteria will select a more stable sample but these patients will remain quite ill and will have the potential to worsen regardless of study participation. We estimate the 5% will die from their acute and chronic medical conditions during the study interval which may last up to 7 days. Another 5-10% will complete the study interval but die from the acute and chronic medical conditions in the 4 weeks after study enrollment. No study that has randomized intubated patients to dexmedetomidine versus another sedative medication has shown an increase in mortality rate.

Pregnant (confirmed by a positive pregnancy test documented in the medical record) or lactating women will be omitted from the study. For women of potentially fertile age, it is standard medical practice on the participating ICUs to rule out pregnancy early in the course of respiratory failure; this information is available in the medical record during the enrollment screening process. If no documentation is present, we will perform a urine or blood test prior to any consent procedures.

Psychological Risks
There is a risk to maintaining confidentiality of any study participant. This risk is thought to be low because Mayo Clinic number and names will only be contained on the written signed consent forms, a data collection form for a home telephone number for follow up contact at 3 and 6 months when discharged from the ICU, and a Health Survey (SF-36) that is electronically scored.

Subjects may perceive an invasion of their privacy when approached for study participation by a member of the research team. This risk is thought to be low given that we will first discuss appropriateness of any potential subject with the

patient-care nurse. There is risk for invasion of privacy when being contacted twice in a 6-month time frame for the post-ICU instrument administration. This risk is thought to be low as participants will be asked to complete the questionnaires over the phone in the convenience of their homes at a time that is convenient for them.

Subjects may feel burdened by responding to the three times daily anxiety assessment via the visual analog scale-anxiety (VAS-A) and the alertness/arousal assessment using the RASS and for the presence/absence of delirium with the Confusion Assessment Method-ICU (CAM-ICU) three times each study day for up to 7 days. This risk is thought to be low given that our experienced study personnel all are well-aware of the energy limitations of ICU patients and will approach them in a gentle, un-hurried manner.

Although post-ICU depression symptoms are common (approximately 25%) the risk of severe depression and self-harm is very low. Since the PHQ-9 can be scored in real-time, if a subject has a score > 10 (indicating moderate depression symptoms), or verbalizes self-harm (PHQ-9 item #9), the phone interviewer will be trained by the investigators to do the following: (1) Acknowledge to the subject that they have some symptoms that might indicate significant depression and were they aware of that. (2) Ask if they have discussed these symptoms with family members or his/her physician. (3) If there are responses indicating serious intent of self-harm and access to lethal instruments, then responses may range from contacting family members (contact numbers will be obtained on subject enrollment) to further intervention such as notifying the subject's primary physician or making a referral call to the county mental health agency. Dialing 911 is always an option in the unlikely event that immediate care is needed.

Alternative Treatments/Procedures

Any subject (or their proxy who enrolled them in the study) enrolled from the participating ICUs is free to withdraw from the study at any time. The alternative treatments/procedures associated with this study for those mechanically ventilated patients who choose not to participate is to continue to receive the standard ICU care for the respective unit, which consists of sedative and opioid therapy administered by and at the discretion of the bed side ICU nurses with medications selected and ordered by the attending ICU physician.

Potential Benefits of the Proposed Research to Human Subjects and Others

Subjects randomized to the SMST group may receive more individually tailored, better control of anxiety through the self-management of anxiety symptoms without over-sedation than those subjects randomized to the usual care group of nurse-administered sedative therapy (NAST). Subjects randomized to the usual care group of NAST may not receive any benefit from participating in this study.

The findings from this study have the future potential to benefit the thousands of patients who receive mechanical ventilatory support each year in the U.S. Potential benefits include greater control of anxiety, fewer days receiving mechanical ventilation, less delirium, and shorter ICUs stays realized from receiving less sedative medication through the self-administration of a sedative medication controlling symptoms and promoting comfort while receiving ventilatory support. Other potential benefits for SMST participants include

better post-ICU physical and functional status, psychological well-being, and health-related quality of life. These potential benefits would parallel the 20 years of research findings surrounding patient-controlled analgesia whereby patients report greater control with pain and high satisfaction when provided the opportunity to self-manage symptoms in many in-patient and out-patient surgical and diagnostic procedures settings.

9. Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents; examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof. The Mayo Clinic will be the primary data storage site for the study and will serve as the coordinating center.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure

was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

The Investigator will retain study records including source data, copies of case report forms, consent forms, HIPAA authorizations and all study correspondence for at least 6 years after the study file has been closed with the IRB.

10. Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study was monitored quarterly at both sites by the University of Minnesota Clinical and Translational Science Institute’s Clinical Monitoring Service (CTMS). As of October 2023, Mayo Office of Research Regulatory Support (ORRS) will complete semiannual monitoring at the Mayo Clinic site only, as study enrollment has been completed at the University of Minnesota. The investigators will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigators will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University and Mayo Clinic compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University and Mayo Clinic compliance and quality assurance offices.

11. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects or his /her legally authorized representative (LAR) to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject or LAR, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or LAR and the investigator-designated research professional obtaining the consent.

12. Study Finances

12.1 Funding Source

This study is financed through a (pending funding) grant from the U.S. National Institutes of Health, National Heart, Lung & Blood Institute 1-R01HL130881-01 Efficacy of self-management of sedative therapy by ventilated ICU patients (L. Chlan and C. Weinert, MPIs).

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual

Conflict of Interest Policy or the Mayo Clinic Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy. All Mayo Clinic investigators will follow Mayo Clinic conflict of interest policy.

12.3 Subject Stipends or Payments

Subjects will receive no payment or stipend for participation in this study.

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