Revised Research Protocol December 10, 2015
2015H0019: Safety, Feasibility, and Acceptability of Patient-Controlled Anxiolysis with Dexmedetomidine (PCA-DEX) for Burn-Care Dressing Changes

Regulatory Sponsor/PI: Larry M. Jones, MD
Associate Professor of Surgery - Clinical
Director, Burn Center
The Ohio State University Wexner Medical Center
410 W. 10th Avenue
Columbus, OH 43210

Sub-Investigators: Claire Murphy, PharmD
Rebecca Coffey, MSN, CNP
J. Kevin Bailey, MD

Kristin Calvitti, MS, RN, ACNSBC, CMSRN

Mahmoud Abdel-Rasoul, MAS

Funding Sponsor: The Ohio State University Center for Clinical & Translational Science (CCTS)

Study Products: Dexmedetomidine: Precedex®

Version / Date: **Version 3/20 April 2018**

CONFIDENTIAL

Study Summary

Title	Safety, Feasibility, and Acceptability of Patient-Controlled Anxiolysis with Dexmedetomidine for Burn-care Dressing Changes
Short Title	Patient-Controlled Anxiolysis.
Protocol Number	The standard protocol number used to identify this study.
Phase	Phase II
Methodology	Study design is an open label, pilot study of patient controlled anxiolysis with dexmedetomidine (PCA-DEX)
Study Duration	Estimated duration for the study is 1 year.
Study Center(s)	The study will involve a single site: The Ohio State University Wexner Medical Center 410 W. 10th Avenue Columbus, OH 43210
Objectives	The primary aim of this pilot study is to establish the safety and feasibility of PCA-DEX during burn care dressings for patients with burn injury. The secondary aim is to determine the acceptability of PCA-DEX for anxiety symptom management by patients with burn injury and nursing staff caring for these patients.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Study subjects will be recruited from patients admitted for initial management of burn injury with >1% total body surface area burn who are able to operate the PCA infusion pump 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®) loading dose of 0.25 mcg/kg intravenously over 10 minutes, initiated 10 minutes prior the start of burn dressing change, followed by a continuous infusion rate of 0.4 mcg/kg/hr by the Alaris® PCA Module. Throughout the dressing change, study patients may self-administer mini-doses (0.1 mcg/kg with a 10 minute pump lock-out). All patients will continue to receive standardized opioid therapy for dressing changes.
Duration of administration	Up to 5 days during burn wound care procedures only

Statistical Methodology	Descriptive statistics will be carried out on categorical demographic, clinical, safety and feasibility data will be summarized as frequencies and percents. Continuous demographic, clinical, procedural pain and procedural anxiety data will be summarized as means and standard deviations. Repeated measurements over time will be summarized at each relevant time point.

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

Pain associated with burn injury is usually high intensity pain and can be extremely challenging for clinicians to adequately manage. In order to improve burn care-related outcomes such as wound closure rates, length of stay, total cost of care, patients are subjected to incredibly painful procedures including debridement, wound care, and physical and occupational therapy. Current practice guidelines recommend early analgesic intervention with a standardized approach for the management of pain associated with burn-care treatments.**(Faucher et al, 2006)** The impact of inadequate control of procedural pain has been associated with psychological complications including increases in anxiety, background pain, and future procedural pain.**(Summer et al, 2007)** The psychological responses of sustained anxiety associated with anticipation of heightened procedural pain or exacerbation of background pain, is associated with an increase in sympathetic activation resulting in the release of catecholamines and changes in local blood flow which lower the nociceptive threshold and sensitize the wound. **(Chapman et al, 1986; Zimmerman, 1984)** Additionally, muscle tension in the area of burn injury can occur with anxiety to an extent that local nociceptors are activated. Anxiety can also potentiate the perception of pain through triggering of higher brain centers and memories of the previous trauma.**(Meyer et al, 2002)** These psychological and physiological factors associated with sustained and significant anxiety intensify in a positive feedback phenomenon known as the "wind-up phenomenon", contributing to the immense challenges of providing adequate pain management and ultimately decreasing quality of life in patients experiencing burn care interventions.**(Chapman et al, 1986)** Multiple dressing changes and treatments over the course of the burn patients recovery can increase fear and anxiety. Patients report feelings of helplessness, and loss of control.**(Esfahlan et al, 2010)** To date, only two studies guide benzodiazepine based anxiolysis during burn dressing changes with inconclusive evidence of effectiveness.**(Bidwell et al, 2012; Patterson et al, 1997)** A limitation of this current practice is that medications are administered at the nurses' discretion based on subjective observations of a patient's anxiety. There is no opportunity for patients to engage in anxiety self-management. Clearly, innovative interventions are needed that are safe and feasible to implement that effectively manage the significant anxiety in patients undergoing burn-care dressing changes.

Numerous studies have demonstrated that patient controlled analgesia in burn patients is beneficial given the patient can self-titrate medication need according to individual requirements that are not controlled by the clinician. **(Prakash et al, 2004; Kinsella et al, 1988)** The wide variations associated with clinician-delivered opioid therapy and the over- and under-treatment of pain can be avoided with this strategy. **(Prakash et al, 2004; Kinsella et al, 1988)**However, there have been no previous investigations of providing patients with the opportunity to self-manage the significant anxiety experienced prior to and during burn-care treatments and dressing changes. One medication that might be ideal for anxiety self-management is dexmedetomidine. Dexmedetomidine (Precedex®) is an α_2-agonist FDA-approved for surgical sedation or procedures. Chlan and colleagues have previously demonstrated the benefits of patient controlled sedation with dexmedetomidine for mechanically ventilated patients' anxiety self-management.**(Chlan et al, 2010)** There is, however, limited examination in of dexmedetomidine the burn population, and there is not known if patient controlled administration of dexmedetomidine is beneficial for burn patients to self-manage their anxiety during painful and distressful burn care treatments.

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 originally 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; the indication for sedation of non-intubated patients prior to and/or during surgical and other procedures was approved later in 2008.

The Alaris® PCA Module with Guardrails® Suite MX Software is an electromechanical infusion pump that uses a stepper motor that exerts pressure on an inserted syringe to control the infusion into a patient. The PCA module is connected to the Alaris®PC unit which is pole-mounted. The PCA module includes an attached patient dose request cord that allows a patient to self-administer medication 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 Alaris®PCA Module with Guardrails® Suite MX Software is indicated for accurate, volumetric, infusion of drugs by continuous or patient-demanded (PCA)

intravenous administration.The Alaris®PCA Module allows patients to self-administer drug within clinician programmed limits and/or hospital-defined medication limits.

2. Study Objectives

2.1 Primary Objective:

The primary aim of this pilot study is to establish the safety and feasibility of patient-controlled anxiolysis with dexmedetomidine (PCA-DEX) during burn care dressings for patients with burn injury.

Feasibility will be defined by:

a) Number and proportion of patients who consent to enrollment
b) Proportion of eligible subjects enrolled prior to first dressing change
c) Number of days on protocol that patients successfully use the PCA device
d) Ability of burn nurses to adjust the pump and adhere to the infusion rates of the PCA-DEX protocol.

Safety will be assessed by:
The proportion of patients successfully completing the pilot trial without adverse effect which include significant hypotension, bradycardia, or agitation from uncontrolled anxiety. Detailed safety monitoring parameters clearly alert the research and burn-nurses of the guidelines for contacting independent physician safety monitors at each site. Hemodynamic compromise (e.g., bradycardia, hypotension), unresolved agitation or inability of any study patient to safely participate in the PCA-DEX protocol are specified reasons the physician safety monitor can stop the protocol and/or remove any subject from the study. The number of patients who develop any of these adverse effects and/ or who require removal from the protocol will be reported.

2.2 Secondary Objectives:

Secondary objectives for the study include:

a) *Patient Acceptability*: Patients will evaluate PCA-DEX in regards to their willingness to use PCS-DEX prior to and during burn dressing changes to self-manage anxiety and their satisfaction ratings with anxiety self-management.
b) *Nurse Acceptability*: The nursing staffs' acceptability of the PCA-DEX protocol for patients' to self-manage anxiety surrounding burn care dressing changes will also be evaluated.

3. Study Design

3.1 General Study Design

The study design will be an open label, single arm, pilot study with all patients receiving standardized opioid therapy plus patient controlled anxiolysis with

dexmedetomidine for burn care dressing changes. The protocol will last up to five days or until the patient exits the study. After 5 days the regimen for burn care dressing changes reverts to usual care with drug choice by the attending physician.

3.2 Primary Study Endpoints

The primary endpoints to be reported in this study includes establishing the feasibility of subject recruitment and protocol adherence to a protocol for PCA-DEX for burn care dressing changes in patients admitted for initial burn care management. Feasibility will be determined by the number and proportion of patients who consent to enrollment, the proportion of eligible subjects enrolled prior to first dressing change, number of days on protocol that patients successfully use the PCA device, and ability of burn nurses to adjust the pump and adhere to the infusion rates of the PCA-DEX protocol.

3.3 Secondary Study Endpoints

The secondary endpoints to be analyzed in this study include evaluation patient and nursing acceptability of the PCA-DEX protocol.

3.4 Primary Safety Endpoints

Potential adverse events associated with PCA-DEX will be monitored 1 hour before through 1 hour after each dressing change. The primary safety endpoints to be measured include the following:

a) Proportion of subjects adverse effects (systolic blood pressure < 90 mmHg, diastolic < 50 mmHg, heart rate < 50 beats/min or respiratory rate <10 breaths/minute) and require protocol suspension or eventual removal for safety reasons from the study for these reasons prior to day 5.

b) Proportion of days with protocol violations related to the drug, pump, or both.

4. Subject Selection and Withdrawal

4.1 Inclusion Criteria

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

1. Patients ages 18- 89 years admitted for initial management of thermal burn injury (flame, scald, contact)
2. Presentation to The Ohio State University Wexner Medical Center Burn Center within 48 hours of burn injury
3. Initial assessment of thermal burn size greater than 1% total body surface area
4. Expected stay of at least 3 days
5. Read, write and speak English
6. Subject 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. Positive pregnancy test or lactation
2. incarcerated
3. Active alcohol withdrawal
4. Current hemodynamic instability (current hypotension systolic blood pressure <100 mmHg, sustained heart rate < 60 beats/min without a pacemaker, symptomatic bradycardia, or second or third degree heart block based on a 6-second electrocardiogram (ECG) waveform verified by two members of the healthcare team proficient in ECG interpretation)
5. Paralysis of other condition preventing patient ability to operate PCA device
6. Acute hepatitis or liver failure
7. Acute stroke or acute, uncontrolled seizures
8. Acute myocardial infarction
9. Severe cognition or communication difficulties (e.g., coma, deafness without signing literacy, dementia, non-English speaking)
10. Chemical or electrical burn.
11. Any condition precluding inclusion at the discretion of the burn surgeons

4.3 Study Exit Criteria

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

1. Subject completes protocol
2. Subject voluntarily withdraws from the study
3. Subject death
4. Subject experiences a serious persistent adverse event such as unexplained rash or sustained adverse effect such as systolic blood pressure < 90 mmHg, diastolic < 50 mmHg, heart rate < 50 beats/min or respiratory rate <10 breaths/minute.

4.4 Subject Recruitment and Screening

Subjects will be recruited from the Burn Center within The Ohio State University Wexner Medical Center (OSUWMC). OSUWMC is the only central Ohio hospital with a commitment to the management of adult burn patients with a 22-bed Burn Center verified by the American Burn Association. Patients range in age from 16-89+ and include injuries from flame, scald, contact, chemical, and electrical mechanisms. The Burn Center admits about 300 patients per year with an average length of stay of 6.3 days (range 1-64).

Informed Consent will be obtained from the patient only. A member of the research team (Coffey, Murphy, Calvitti, Uribe) will review the patient census on the Burn Center each morning with the unit's charge nurse to determine if there are any patients who meet the study inclusion criteria. All of these individuals are employed at the OSUWMC. If any patient on the Burn Center meets the inclusion criteria, the responsible member of the research team listed above will then discuss the potentially eligible patient with either Dr. Jones or Dr. Bailey, who will make the

final determination about the patient's eligibility. If Dr. Jones or Dr. Bailey determines the patient is study eligible, he/she will then be approached for consent and potential enrollment into the study. Given all patients are in-patients on the Burn Center, recruitment will take place in the privacy of the hospital room before any scheduled burn care dressing changes in the procedure room.

If a patient is willing to hear more information about the study, the responsible member of the research team will explain to the patient that a study is being conducted to examine whether a medication administered by patients' themselves to manage anxiety during the burn care dressing changes is feasible, safe and acceptable to patients. Patients who decide to participate in the study will self-administer dexmedetomidine (Precedex ©), a medication approved by the Food and Drug Administration (FDA) to help manage anxiety during medical procedures. Our study is interested in examining whether patients themselves can and will self-administer this medication during the burn care dressing changes. Patients will be told that the nurses caring for them on the Burn Center will continue to provide pain medication per the routine physician orders on the unit. Patients will be told that the decision whether or not to participate in the study will not affect their care on the Burn Center in any way. If the patient is interested in participating in the study, a copy of the consent form will be provided to the patient prior to the scheduled burn care dressing change. Patients will be asked to read the consent form, ask any questions they may have about the study with the responsible member of the research team. Ample time will be given for any patient to consider study participation prior to the scheduled time for the first dressing change in the procedure room on the Burn Center. Given the study inclusion criteria, patients will only be approached once for study participation given our aim is to examine PCS-DEX beginning with the <u>first</u> burn care dressing change, up to 5 days on the Burn Center. If the patient provides consent, the HIPAA form will next be presented to allow the research team to collect information from the patient and from the medical record. If the patient declines to participate in the study, he/she will be thanked for their time and will not be approached again during hospitalization on the Burn Center.

4.5 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 hospital discharge, they will be transitioned to standard regimen for burn care dressing changes at the discretion of the attending burn surgeon. Any patient who elects to withdraw from the PCA-DEX protocol or is withdrawn prior to completing of the 5 day protocol will be closely

monitored for an additional 24 hours for any adverse events. 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 utilize a dosing algorithm consisting of a loading dose (0.25 mcg/kg) administer over 10 minutes, initiated 10 minutes prior to the start of burn wound care, followed by a continuous basal infusion of 0.4 mcg/kg/hr with 6 allowable patient-controlled self-boluses per hour (0.1 mcg/kg) each with a 10-minute lock-out. The Lifecare PCA® Infusion System is the infusion pump used at OSUWMC for patient controlled analgesia. The pump will be utilized in the PCA + continuous mode. Flow rates based on a 30 mL syringe range from 0.1-650 ml/hr (0.1-9.99 ml/hr in 0.1 ml/hr increments, 10-99.9 ml/hr in 0.1 ml increments and 100-650 ml/hr in 1 ml increments. Delivery accuracy is ± 2% of full scale plunger travel not including syringe variation. 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 Investigational Drug Service (IDS# M-1429) within OSUWMC. When study drug is requested for a subject, IDS will coordinate the preparation and dispensing of dexmedetomidine using a supply designated for this study. Required paper work will be completed.

For patients weighing up to 88 kg, under strict aseptic technique, 200 µg/2 ml will be added to 28 ml of 0.9% sodium chloride; this will yield a concentration of 200 µg/30 ml (or 6.7 µg/ml). Dexmedetomidine will be delivered via a pharmacy-prepared 30 ml syringe for use with the Alaris®PCA Module as described above. Preparation date and time will be recorded.

For patients weighing more than 88 kg, under strict aseptic technique, 400 µg/4 ml will be added to 26 ml of 0.9% sodium chloride; this will yield a concentration of 400 µg/30 ml (or 13.3 µg/ml). Dexmedetomidine will be delivered via a pharmacy-prepared bar-coded syringe manufactured for use with the Alaris®PCA Module as

described above. Preparation date and time will be recorded.

All dexmedetomidine preparation will be performed in accordance with USP 797 standards.

5.4 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person in the IDS accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files.

5.5 Storage

Dexmedetomidine will be controlled by the Investigational Drug Service, a secure pharmacy service at OSUWMC. The study drug will be stored in a secure, limited access location separate from commercial drug supplies. The investigational dexmedetomidine supply will be stored at a controlled room temperature not exceeding 25 °C (77 °F) with excursions allowed between 15 to 30 °C (59 to 86 °F). The study drug is not light sensitive and requires no additional special storage conditions. Each dose will be signed out of the IDS log with the lot number of each 200 µg/2 ml clear glass vial used to prepare the syringe for the study patient. Vials are intended for single-use only.

5.6 Study Drug Accountability

Study drug accountability will be performed to document activity dates, drug receipt, dose and number of vials of drug dispensed, subject initials and subject ID number to whom drug dispensed, running inventory and disposition of expired or unused drug. Accountability will be accomplished by using institutional drug accountability forms and/or an electronic accountability system.

6. Study Procedures

Dexmedetomidine PCA Protocol: The PCA-DEX dosing algorithm will consist of a loading dose (0.25 mcg/kg) given intravenously over 10 minutes, administered 10 minutes prior to the start of burn wound care, followed by a continuous basal infusion of 0.4 mcg/kg/hr with 6 allowable patient-controlled self-boluses per hour (0.1 mcg/kg) each with a 10-minute lock-out. Drs. Larry Jones and J. Kevin Bailey or their designate will write the PCA-DEX medication orders. Subjects will receive standard opioid therapy (oral oxycodone/acetaminophen 5/325 mg 60 min. prior and IV morphine 4-12 mg or hydromorphone IV 0.5-1.5 mg 5 to 10 min. prior and buccal fentanyl 400 mcg as needed

during burn wound care) and can receive bolus supplemental sedative medications (benzodiazepines) as ordered by Drs. Jones or Bailey if needed in the judgment of the burn-care nurse. Subjects will be monitored closely by research personnel during the first burn wound care session from 1 hour prior to 1 hour after completion of burn wound care. Every heart rate and blood pressure recordings will be abstracted from the medical record from 1 hour prior to through 1 hour after completion of the daily burn wound dressing changes for days 1 through 5. 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 and independent safety monitor include: heart rate (HR) < 55 beats per min sustained for > 10 min; systolic BP < 90 mm Hg or >140 mm Hg sustained for >10 minutes; diastolic BP < 50 mm Hg or >90 mm Hg sustained for >10 minutes, respiratory rate < 10 breaths per minute sustained for >10 minutes or oxygen saturation <92% sustained for >10 minutes; or persistent inability to understand rationale for triggering the PCA device despite education and demonstration.

If the study subject has evidence of sustained hemodynamic instability (HR<60 bpm, SBP <90 mmHg or DBP < 50 mmHg) during the daily pre-procedure assessment, the patient will not be eligible to receive study drug on that day. For that day the patient will receive standard of care as appropriate instead of the study intervention. The patient will then be reassessed prior to the subsequent study days to determine eligibility for study drug up through day 5.

Data Collection Measures and Procedures

Study entry demographic and descriptive data: Data to be recorded includes: age, gender, race, ethnicity, admission weight, severity of burn injury, burn etiology, total body surface area burned and depth of injury, and all home and hospital medications.

Daily Measures on Protocol. The following will be obtained from enrolled patients each day by a member of the research team.

Overall anxiety and pain. The abbreviated Burn Specific Anxiety and Pain Scale (BSAPS) on day 1, 1 hour prior to the first burn dressing change. **(Taal et al, 1999)**

Procedural Anxiety. Anxiety, defined as a state marked by apprehension, agitation, increased motor activity, arousal, and fearful withdrawal will be obtained from subjects. **(McCartney et al, 1994)** Patients will evaluate current anxiety level 1 hour before and 1 hour after each burn dressing change using a 100-mm Visual Analogue scale-anxiety (VAS-A). **(McCartney et al, 1994; Hornblow et al, 1976)**

Subjects will be asked to rate their current level of anxiety on the VAS-A in response to, "How anxious are you feeling today?" 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. **(Cline et al, 1992; Gift, 1989)** 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. **(Bergbom-Engberg et al, 1989; Knebel et al 1994)** Reason(s) for not obtaining a daily anxiety assessment will be recorded. The proportion of those assessments completed and reasons for non-completion will be used to inform strategies to minimize missing data for our planned randomized clinical trial.

Procedural Pain. Patients' will evaluate current pain level 1 hour before and 1 hour after each burn dressing change using a 100-mm Visual Analogue Scale-Pain. **(McCartney et al, 1994)** Patients will be asked to rate their current level of pain on the VAS-P in response to "How much pain are you having right now?" A 100-millimeter vertical line will be anchored on each end by statements of 'no pain at all' to 'the most pain I have ever experienced'. As with the VAS-A, the vertical orientation has been chosen due to increased sensitivity and ease of use for patients. **(Cline et al, 1992; Gift, 1989)** Subjects will be asked to mark their current pain 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. **(Bergbom-Engberg et al, 1989; Knebel et al 1994)** Reason(s) for not obtaining the pain assessments will be recorded. The proportion of those assessments completed and reasons for non-completion will be used to inform strategies to minimize missing data for our planned randomized clinical trial.

Protocol adherence. A checklist will be completed daily to monitor the number of days subjects are able to use the PCA device for up to 5 days. A checklist will also be used to monitor the ability of the burn-nurses to adhere to the PCA protocol per instructions.

Daily adverse event monitoring. Research staff will record and report the presence of hypotension, bradycardia (known adverse effects of dexmedetomidine), and protocol deviations related to drug, pump or both. Heart rate and blood pressure will be abstracted from the medical record. Research team staff or burn-nurses caring for PCA-DEX subjects will alert the attending physician and the safety monitor for HR < 55 bpm sustained for > 10 min; systolic BP < 90 mm Hg or >140 mm Hg sustained for >10 minutes; diastolic BP < 50 mm Hg or >90 mm Hg sustained for >10 minutes, respiratory rate < 10 breaths per minute sustained for >10 minutes or oxygen saturation <92% sustained for >10 minutes during the period 1 hour prior through 1

hour after completion of burn wound dressing change on days 1-5 for any necessary intervention or protocol withdrawal.

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

7. Statistical Plan

Statistical analysis will be carried out on categorical demographic, clinical, safety and feasibility data will be summarized as frequencies and percents. Continuous demographic, clinical, procedural pain and procedural anxiety data will be summarized as means and standard deviations. Repeated measurements over time will be summarized at each relevant time point.

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 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Assessment of Severity and Causality for Adverse Events

Each adverse event will be assessed for severity based on the criteria below.

Severity Grading for Assessment of Adverse Events

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Bradycardia - beats per minute	50 – 54	45 – 49	< 45	Requirement intervention (e.g. pacer or atropine), emergency rapid response activation or transfer to a higher level of care (e.g. intensive care unit or progressive care unit)
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	Requirement for medication for hypertension as assessed by burn physician or transfer to a higher level of care (e.g. intensive care unit or progressive care unit)

Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Requirement for medication for hypertension as assessed by burn physician or transfer to a higher level of care (e.g. intensive care unit or progressive care unit)
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Requirement for intravenous fluids, vasopressor agents rapid response activation or transfer to a higher level of care (e.g. intensive care unit or progressive care unit)
Hypotension (diastolic) – mm Hg	45-49	40-44	<40	Requirement for intravenous fluids, vasopressor agents emergency rapid response activation or transfer to a higher level of care (e.g. intensive care unit or progressive care unit)
Respiratory Rate – breaths per minute	12-17	8-12	<8	Requirement for reversal agent (e.g. naloxone), rapid response activation or intubation
Oxygen saturation, %	85-91	80-85	<80	Requirement for reversal agent (e.g. naloxone), emergency rapid response activation or intubation

In addition, all adverse events will be assessed for causality using the World Health Organization-Uppsala Monitoring Center (WHO-UMC) standardized case causality assessment system as indicated below:

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

8.3 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.

8.4 Reporting of Serious Adverse Events

8.4.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of finding out of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Larry M. Jones, MD 614-293-5710 office
614- 293-3472 fax

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information of ongoing serious adverse events should be provided promptly to the study sponsor.

8.4.2 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.4.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

Agency	**Criteria for Reporting**	**Timeframe**	**Form to Use**	**Submission address/fax numbers**
OSU IRB	SAE: fatal, life-threatening or serious, unexpected, at least possibly related	Within 48 hours for SAE resulting in death Within 7 days for SAE that are life-threatening and unanticipated.	Event Reporting Form version 3.2	Online submission
FDA	SAE: fatal, life-threatening, unexpected, at least possible related	7 calendar days	FDA prefers MedWatch 3500a Form but alternative formats are acceptable (e.g. summary letter)	Fax: 1 (800) FDA - 0178
	SAE: serious, unexpected, at least possibly related	15 calendar days		

8.5 Stopping Rules

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

- Sustained (>30 min.) adverse effects defined by systolic blood pressure < 90 or > 180 mmHg, diastolic blood pressure < 50 or > 100 mmHg; heart rate < 50 or > 120 beats/min. or respiratory rate <10 breaths/min.
- Persistent inability to understand rationale for triggering the PCA device despite education and demonstration

Any subject who experiences any of the above will first be evaluated by the attending physician (or his/her designate) and then the safety monitor. The safety monitors will communicate their findings to Dr. Jones and their opinion of any event(s) regarding the suitability of an individual subjects to continue on the study protocol. Dr. Jones will review the circumstances and will decide whether to restart the protocol or withdraw the subject from the protocol.

Stopping rules for the study (not for individual subjects) will be determined by an independent DSMB after final review of the protocol. Since this is a feasibility pilot study with no comparator arm, study stopping criteria would likely be focused on adequate rates of recruitment, rates of study withdrawal due to subjects not being able to use the PCA device and differences in serious adverse event rates (but setting the level of significance to a stringent level because of the small sample size).

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at the study 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 (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.7 Independent Data and Safety Monitoring Board

A Data Safety Monitoring Board will be established for this study by Dr. Jones and Dr. Chlan. The Board will consist of a minimum of 4 individuals, including a physician/surgeon, pharmacist, nurse-researcher, and statistician. All members will be independent of the study protocol and research team.

We will constitute an independent **Data Safety Monitoring Committee** for this study. Members include the following:

David Evans, MD	DSMC Chair and Surgeon Wexner Medical Center
Michele Balas, PhD, RN, BC-NP, CCRN	Associate Professor, College of Nursing
Tony Gerlach	Pharmacist, Surgical ICU Wexner Medical Center
Larry Jones, MD, ex officio, non-voting	Director, Burn Unit Wexner Medical center The Ohio State University Principal Investigator and IND Sponsor
Kevin Bailey, MD, ex officio, non-voting	Burn Surgeon Wexner Medical center The Ohio State University Investigator
Linda Chlan, PhD, RN, FAAN, ex officio, non-voting	Professor, College of Nursing Co-Principal Investigator
Claire Murphy, Pharm D, Ex officio, non – voting	Pharmacist Wexner Medical Center The Ohio University Investigator
Rebecca Coffey, MSN, RN, CNP Ex officio, non-voting	Nurse coordinator Wexner Medical Center The Ohio State University Investigator

Data Safety Monitoring Committee (DSMC)

At predetermined intervals during the course of the trial, the DSMC responsibilities are the following:

1. Review the clinical protocol, informed consent documents and plans for data and safety monitoring;
2. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome;
3. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
4. Review, make recommendations and assist in the resolution of problems reported by the PI;
5. Protect the safety of the study participants:
6. Report on the safety and progress of the study;

7. Make recommendations to the PI, FDA, and/or the IRB concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of PCS-DEX;
8. Ensure the confidentiality of the study data and the results of monitoring;
9. Assist the PI by commenting on any problems with study conduct, enrollment, sample size, and/or data collection.

The DSMC will be comprised of one independent OSUMC physician, College of Nursing faculty, and SICU PharmD. Each will have one vote. One will be named Chair of the Committee (Dr. Evans). The PI, IND holder (Dr. Jones), and members of the research team from The Ohio State University will be ex officio non-voting member. The Chair of the committee is responsible for documenting decisions to continue and is responsible for issuing meeting minutes.

For this study, 20 subjects will be enrolled. The DSMC will review the outcomes including the safety data after each group of 5 subjects. The DSMC will review safety data collected in each group at a quarterly Safety Review Meetings (SRM). At each meeting, the DSMC members will discuss the safety data. These discussions will include, but are not limited to, details of any adverse events of clinical relevance that raise concern about next cohort, any clinically significant changes in subject vital signs. The DSMC will decide if the study will continue. The decision will be based on consideration of the clinical significance of all relevant endpoints. Authorization to proceed will be obtained in a document signed and dated by the Chair of the DSMC and maintained in the study files. If the safety profile is unacceptable, no new subjects will be enrolled. In this case, the DSMC Chair will document the scientific rationale for the decision based on the safety data and recommendations of the DSMC. The Investigators will review the documentation and provide written agreement not to proceed with the trial. If there are no safety concerns after each review, the study may proceed. The decision to proceed must be by unanimous favourable vote.

Process of safety monitoring
Meetings of the SRC will take place after quarterly or after each group of 5 subjects are available. The Chair may call *ad hoc* DSMC meetings.

Safety Evaluation
The group safety review data will consist of data collected from Screening until Day 5 inclusive. The following data will be presented:

Adverse Events
Vital signs

Safety data (adverse events and vital signs data) will be provided to DSMC members by the PI as soon as it becomes available.

If any SAE(s) occurred in the group under review, the SAE forms and narrative summaries will be presented as well; the SAE documentation will be provided by the PI for distribution to other committee members. All voting members of the DSMC must be present at the meeting. A negative vote on going forward by any of the voting members of the DSMC will place the study on hold pending further review and discussion or terminate the study.

The Chair of the DSMC will prepare meeting minutes summarizing the discussion and detail the outcome of the vote pertaining to the continuation of the study. The minutes will specify the decision of each individual member of the DSMC and the overall decision of the DSMC. A copy of the minutes will be distributed to all members of the DSMC within one working day of the meeting.

Immediately following the DSMC meeting (*i.e.*, within one day of the meeting) the Chair will send the report to the PI for distribution to all members of the DSMC as well as the IRB and FDA, as appropriate. At the end of the study all DSMC documents will be forwarded to the PI for inclusion in the study files.

All SAEs will be reported immediately (within 24 hours of their occurrence). This can be done by faxing a completed SAE Fax Cover Sheet and SAE CRF and by direct telephone communication to the CCTS, IRB, or FDA. A completed SAE Fax Cover Sheet and SAE CRF will follow all telephone reports within 24 hours.

Any SAEs, including death due to any cause, which occurs to any patient entered into this study, whether or not considered related to the investigational product, will be reported within 24 hours to the Sponsor (CCTS) or their representative. A completed SAE Fax Cover Sheet and SAE CRF will follow all telephone reports within 24 hours. All patients with SAEs will be followed up for outcome by Ms. Coffey.

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.

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 5 years after the study file has been closed with the IRB.

10. Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored by the OSU Center for Clinical and Translational Science (CCTS) Study Monitoring Service in accordance with the Standard Operating Procedures (Appendix 5-B). The investigator will allocate adequate time for such monitoring activities which are to promote study participant safety, regulatory and protocol compliance, and data integrity. The extent of these activities will be commensurate with the level of risk and complexity that the study poses. In order for these activities to occur, 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 investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University 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 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 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, 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, and the investigator-designated research professional obtaining the consent.

12. Study Finances

12.1 Funding Source

This study is financed through a pilot grant from The Ohio State University Center for Clinical & Translational Science.

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 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 COI (Conflict of Interest) at least once per year. Faculty and staff should also update their COI 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 OSUWMC and OSU investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

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

13. Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.