DEXMEDETOMIDINE OPIOID SPARING EFFECT IN MECHANICALLY VENTILATED CHILDREN (DOSE TRIAL):

A Phase 1b, Multicenter, double blind randomized controlled dose escalating trial of fentanyl vs. fentanyl + dexmedetomidine as the initial regimen for maintenance of sedation in mechanically-ventilated, critically ill children

Protocol Number: TIN-DOSE-01

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with the International Council for Harmonisation Good Clinical Practice (ICH GCP).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____
Print/Type Name

Principal Investigator Signature / Date: _____
Signature / Date

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: **D**exmedetomidine **O**pioid **S**paring **E**ffect in Mechanically Ventilated Children (DOSE Trial)

Study Description: Multicenter, double blind randomized controlled dose escalating trial of fentanyl vs. fentanyl + dexmedetomidine as the initial regimen for maintenance of sedation in mechanically-ventilated, critically ill children.

This trial will evaluate the opioid-sparing effect of dexmedetomidine when administered with fentanyl to mechanically ventilated, critically ill children. Study drug or placebo will be administered with fentanyl, which will be titrated to achieve sedation scores consistent with response to light touch. Plasma samples and bedside assessments for pain, sedation, and delirium will be collected.

Objectives:

Primary:

- Characterize the opioid-sparing effect of dexmedetomidine when co-administered with fentanyl in children receiving mechanical ventilation.

Secondary:

- Characterize the exposure response relationships of fentanyl and dexmedetomidine when administered alone or in combination in children receiving mechanical ventilation.
- Characterize the safety profile of fentanyl and dexmedetomidine when administered alone or in combination to children receiving mechanical ventilation.

Exploratory:

- Estimate the incidence of intensive care unit delirium in children exposed to fentanyl and dexmedetomidine alone or in combination when receiving mechanical ventilation.

- Estimate the incidence of opioid withdrawal syndrome in children exposed to fentanyl and dexmedetomidine alone or in combination when receiving mechanical ventilation.

Endpoints:	Primary: • Mean hourly dose of fentanyl in mcg/kg/hr during the period of blinded study drug administration Secondary • Sedation based on SBS, RASS scales relative to fentanyl and dexmetetomidine plasma concentrations (Cmax, Cmin,Css) and area under the concentration time curve (AUC) • Incidence of SAEs, and safety events of special interest including clinically significant episodes of hypotension, bradycardia, urinary retention Exploratory • Average, maximum, and minimum daily CAPD scores; Average, maximum, and minimum daily WAT-1 scores; Use of alternative analgesics for withdrawal.
Study Population:	Up to 48 children, 0 to<18 years of age, receiving or with planned receipt of mechanical ventilation
Phase:	1b
Description of	Approximately 20 centers in the United States
Sites/Facilities Enrolling Participants:	Trial participants will be enrolled from pediatric multidisciplinary and cardiac intensive care units.
Description of Study Intervention:	Participants will be randomized to receive placebo or Dexmedetomidine in one of 3 dose escalating cohorts assessed for safety between each cohort 1) Cohort 1: Fentanyl standard of care (SOC) titrated to sedation + saline placebo (bolus + infusion) vs. Dexmedetomidine (0.5mcg/kg bolus load + 0.2mcg/kg/hr infusion) 2) Cohort 2: Fentanyl standard of care (SOC) titrated to sedation + saline placebo (bolus + infusion) vs. Dexmedetomidine (0.5mcg/kg bolus load + 0.5mcg/kg/hr infusion) 3) Cohort 3: Fentanyl standard of care (SOC) titrated to sedation + saline placebo (bolus + infusion) vs. Dexmedetomidine (0.5mcg/kg bolus load + 0.7mcg/kg/hr infusion)
Study Duration:	Approximately 12 months for enrollment
Participant Duration:	Up to 28 days or discharge from ICU

1.2 SCHEMA

Enrollment

Total 48: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.

Baseline

Perform baseline assessments: targeted medical history, demographics (race/ethnicity, age, sex), concomitant medications of interest, pain, sedation and delirium scores, selected laboratory assessments, selected details of clinical course.

Participants enrolled into **cohort 1** and randomized

Cohort 1	Fentanyl SOC	+	Placebo	Vs.	Dexmedetomidine 0.5mcg/kg bolus + 0.2mcg/kg/hr infusion
			N=4		N=12

Participants enrolled into **cohort 2** and randomized

Cohort 2	Fentanyl SOC	+	Placebo	Vs.	Dexmedetomidine 0.5mcg/kg bolus + 0.5mcg/kg/hr infusion
			N=4		N=12

Participants enrolled into **cohort 3** and randomized

Cohort 3	Fentanyl SOC	+	Placebo	Vs.	Dexmedetomidine 0.5mcg/kg bolus + 0.7mcg/kg/hr infusion
			N=4		N=12

Treatment Period (from first day of treatment through 7 days or until extubated, whichever comes first)

Daily fentanyl dose recording, PK sampling, concomitant medications of interest, selected laboratory assessments, pain, sedation, and delirium scores, selected details of clinical course, adverse events

Short term follow-up, (up to 28 days or ICU discharge)

Documentation of analgesic use and dose in mcg/kg daily for 7 consecutive days, then 7 days and 14 days later if not discharged sooner.
WAT-1 scores and adverse events

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Up to 7 days before Day 1	Treatment Day 1 up to Day 7 or extubation, whichever comes first	Short-Term Follow-up End of Treatment Period for 7 consecutive days then 7 days later then 14 days later (±1 days)[a]	Notes Baseline can be Day -1 (if at screening) or on Day 1
Informed consent	X			
Inclusion and exclusion criteria	X	X		
Demographics	X			
Targeted Medical history	X	X		Should include history of genetic abnormality or known congenital cardiac disease incurred prior to study drug administration:
Randomization		X		
Administer study intervention		X		Must document date, time, method, and dosing of fentanyl administration and date and time of blinded study therapy administration
Concomitant medication review	X	X		Concomitant medications of interest (Appendix) should be documented for up to 48 hours prior to study drug initiation, and through extubation or day 7 (whichever is earliest); withdrawal medications of interest should be recorded during the short-term follow-up period
Post-Operative Status		X		
Targeted Physical exam		X		Should include documentation of height and weight
Primary outcome assessment: mean hourly dose of fentanyl (mcg/kg/hr)		X		Assess the primary outcome during the period of blinded study drug administration
Pain Scores (FLACC)[d]		X		Baseline FLACC can be completed up to 24 hours prior to the administration of study drug. Assessments during treatment should be done twice a day as close to PK sample as possible (+/- 1 hour of PK samples).
Sedation scores (SBS, RASS)[d]		X		Baseline SBS, RASS can be completed up to 24 hours prior to the administration of study drug. Assessments during treatment should be done twice a day as close to PK sample as possible (+/- 1 hour of PK samples).
Delirium scores (CAPD)[d]		X		Baseline CAPD can be completed up to 24 hours prior to the administration of study drug. Assessments during treatment should be done twice a day as close to PK sample as possible (+/- 1 hour of PK samples).
Biologic sample collection: PK sampling		X		Should occur twice daily up to 7 days; 0.5ml per sample; samples should be drawn relative to initiation of fentanyl infusion, change in fentanyl dosing, or bolus administration of fentanyl
Record laboratory assessments		X		Record the baseline laboratory assessments obtained per standard of care and values closest to study drug initiation (WBC count,

				ESR, CRP, creatinine, BUN, albumin, AST, ALT, serum electrolytes (Na, K, Cl, HCO3).
Ventilation/Respiratory Support Information		X		This is to include mode of ventilator support, and PEEP, PIP, FiO2 closest to study drug initiation only
Withdrawal drug administration		X	X	Should include drugs and dosing for treatment of withdrawal from previous 24 hour time period
Record details of clinical course		X	X	Should include information on date/time of extubation, date/time of ICU discharge; and the presence of sepsis or shock[b]
Adverse event review and evaluation		X[c]	X	
Events of Special Interest		X	X	Should include hypotension, bradycardia, and urinary retention per study-specific definitions
Withdrawal scores (WAT-1)[d, e]			X	Assessments should occur twice a day (ex at 0800 and 2000)

a. Short term follow up may begin prior to day 8 if extubated sooner
b. Record presence of sepsis or shock at baseline enrollment visit only, not during treatment or short term follow up period
c. Record and evaluate any new AE or condition not previously recorded at the screening visit and occurring prior to first dose of study drug
d. Daily assessments and WAT-1 scores that are missed will not be considered a protocol deviation
e. The WAT-1 is not required if additional sedation is needed at the time of study drug discontinuation

AST=aspartate aminotransferase; ALT=alanine aminotransferase

2 INTRODUCTION

2.1 STUDY RATIONALE

Treatment of pain and maintenance of sedation are common requirements for the management of critically ill children including those receiving mechanical ventilation. These goals often require significant exposure to opioid and other sedative and analgesics, with potential detrimental neurologic effects, including drug dependence, iatrogenic withdrawal, and delirium. Multiple drug combinations are commonly used and routine management of sedatives and analgesics in critically ill children is highly variable.

Preliminary data suggest that the addition of dexmedetomidine to opioid-based sedation and analgesia may have a synergistic and opioid-sparing effect while maintaining adequate sedation and pain control. In turn, reduced exposure to opioids during mechanical ventilation may contribute to decreased risk of iatrogenic withdrawal and delirium.

We plan to conduct a randomized clinical trial to determine the opioid-sparing effect of dexmedetomidine when added to fentanyl-based sedation regimen in critically ill children. This trial will prove the feasibility of blinding and randomization, obtaining requisite plasma samples to allow measurement of drug exposure, refine the methodology to assess withdrawal during mechanical ventilation, and provide preliminary information to guide the power calculations and dose selections for the future trial.

2.2 BACKGROUND

Pain and agitation are common among mechanically ventilated children

Pain and agitation are commonly reported among mechanically-ventilated children and adults, and have been associated with the presence of the endotracheal tube, underlying medical conditions, procedures, and routine care interventions such repositioning, tracheal suctioning, and line removals. Because pain and agitation are such ubiquitous experiences in the intensive care unit setting and can be major causes of distress, clinical care guidelines recommend routine assessment and management of pain and agitation during critical illness.[1-7]

Opioids are frequently used first line for analgesia and sedation of critically ill children. Initial management of pain and agitation among critically ill children most often consists of opioids such as morphine or fentanyl, administered as intermittent or continuous infusion and titrated to desired effect.[8] Although administration of opioids has proven beneficial to accomplish goals of maintaining mechanical ventilation and decreasing oxygen consumption, the dose and duration of opioids in the intensive care unit setting have been associated with development of iatrogenic withdrawal syndrome and delirium.[9,10] Iatrogenic withdrawal syndrome is associated with longer duration of mechanical ventilation, prolonged intensive care unit and hospital stays, and prolonged medication administration.[10] Delirium, a syndrome of acute brain dysfunction, has been associated with up to 85% increase in pediatric ICU costs, post-traumatic stress disorder, neurocognitive dysfunction after hospital discharge, and an independent, increased risk of mortality during and after hospitalization.[11-14]

Limiting opioid exposures in critically ill children may result in decreased risk for adverse outcomes of iatrogenic withdrawal syndrome and delirium.[16] However, it is not currently known how opioid sparing may be accomplished while maintaining adequate pain control and sedation, or whether opioid sparing

efforts will lead to the downstream desired effects. One strategy to limit opioid exposures may be to combine drugs with potentially synergistic properties, such as fentanyl and dexmedetomidine. ***Fentanyl*** is a high potency synthetic opioid (~100-300x more potent than morphine) that mediates its analgesic effect through interaction with mu opioid receptors at pre-and post-synaptic sites in the central nervous system [17-19]. Owing to its high lipophilicity in comparison to morphine (octanol/water solubility ratio 816 vs. 1.4), fentanyl readily penetrates the central nervous system from plasma, eliciting a fast onset of action (1.5 minutes) [18,20]. As an opioid receptor agonist, fentanyl mimics endogenous peptide opioid ligands such as enkephalins, endorphins, and dynorphins. Following receptor interaction, potassium conductance of the cell membrane is enhanced, which ultimately leads to axonal hyperpolarization and/or calcium channel inactivation and a subsequent decrease in neurotransmitter release. ***Dexmedetomidine*** is a central alpha-2 receptor agonist with sedative, analgesic, anti-shivering, sympatholytic, and anxiolytic properties. It is highly selective for alpha -2 receptors, has a short distribution half-life of only 6 to 7 minutes, and readily distributes into multiple tissues, including across the blood-brain barrier into the CNS. Dexmedetomidine exerts its hypnotic action through activation of central pre- and postsynaptic α2-receptors in the locus coeruleus, thereby inducing a state of unconsciousness similar to natural sleep, with the unique aspect that recipients remain easily rousable and cooperative.[21]

Dexmedetomidine has previously been associated with opioid-sparing effects and reduced risk of delirium. In prior studies, dexmedetomidine reduced the requirements of other anesthetics and analgesics including inhalational anesthetics, propofol, thiopental, and fentanyl.[22,23] A modest perioperative opioid sparing effect of dexmedetomidine has also been described in adolescents and adults, including after cranial, spinal, and abdominal surgery.[24-26] Independent of its opioid-sparing effects, dexmedetomidine administration to critically ill children may lead to decreased risk of delirium in this population. Dexmedetomidine administration to critically ill adults has been associated with reduced risk of delirium, believed secondary to its induction of more physiologic sleep-wake cycle. In a double blind randomized controlled trial of 104 critically ill adults, continuous use of dexmedetomidine for up to 5 days results in more delirium free days compared to lorazepam.[27] Finally, in children, intraoperative dexmedetomidine administration reduced the risk of emergence delirium,[28-30] but its effect on intensive care unit delirium in children has not been systematically evaluated.

We propose to determine the opioid-sparing effect of combination therapy with fentanyl and dexmedetomidine compared to fentanyl alone to mechanically ventilated, critically ill children. Characterization of this effect and collection of data regarding plasma drug exposures, and pain, sedation, delirium, and withdrawal scores will provide the necessary information to design the definitive trial towards optimization of pain and sedation management in critically ill children.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Known potential risks are those associated with drug administration and blood draws. In addition, there is a potential risk of loss of confidentiality and it will be minimized per plan described below in this protocol (section 10.1.3).

2.3.2 KNOWN POTENTIAL BENEFITS

Participation in this trial has no potential benefits to the participant beyond the potential therapeutic benefit derived from the use of the study drug. The results of this trial may benefit children in the future who require sedation and analgesia for mechanical ventilation.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Fentanyl and dexmedetomidine are two of the most commonly administered drugs to mechanically ventilated children in the intensive care units (ICU) participating in this trial. There is clinical equipoise regarding sedative and analgesic administration and no definitive guidelines to assist in the management of these drugs in critically ill children. Because our trial allows titration of fentanyl per standard of care and administers blinded dexmetetomidine within the approved doses on the drug product label, the trial procedures do not notably depart from standard of care. Therefore, there is minimal additional risk to participants.

Many critically ill children supported with invasive mechanical ventilation have indwelling catheters. This will reduce the need for blood draws and the associated risks. For participants without indwelling lines, we will attempt to coordinate trial-specific lab draws with labs drawn per standard of care.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Characterize the opioid-sparing effect of dexmedetomidine when co-administered with fentanyl in children receiving mechanical ventilation	Mean hourly dose of fentanyl in mcg/kg/hr during the period of blinded study drug administration	Characterization of differences between dosing exposures for the four groups will allow estimation of the opioid-sparing effect of dexmedetomidine.
Secondary		
Characterize the exposure response relationships of fentanyl and dexmedetomidine when administered alone or in combination in children receiving mechanical ventilation	Sedation based on SBS, RASS scales relative to fentanyl and dexmetetomidine plasma concentrations (C_{max}, C_{min},Css) and area under the concentration time curve (AUC)	PK is known to be altered in children compared to adults, and in those with critical illness. Characterization of pharmacokinetic-pharmacodynamic relationships can improve dose optimization when dose may not be equivalent to plasma exposure and related effect.
Characterize the safety profile of fentanyl and dexmedetomidine when administered alone or in combination	Incidence of SAEs, and safety events of special interest including clinically significant	Safety

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
to children receiving mechanical ventilation	episodes of hypotension, bradycardia, urinary retention	
Tertiary/Exploratory		
Estimate the incidence of intensive care unit delirium in children exposed to fentanyl and dexmedetomidine alone or in combination when receiving mechanical ventilation	Average, maximum, and minimum daily CAPD scores	Measures of delirium
Estimate the incidence of opioid withdrawal syndrome in children exposed to fentanyl and dexmedetomidine alone or in combination when receiving mechanical ventilation	Average, maximum, and minimum daily WAT-1 scores Use of alternative analgesics for withdrawal.	Measures of withdrawal

4 STUDY DESIGN

4.1 OVERALL DESIGN

- Hypothesis: Mean hourly fentanyl dose will be reduced by ≥25% by the addition of dexmedetomidine to fentanyl therapy.
- Phase 1b
- Randomized, double blind placebo controlled dose escalation trial of sedation regimens in critically ill children

Table 1: dosing cohorts

COHORT	PLACEBO (N=12)	Dexmedetomidine (N=36)
1	N=4	dexmedetomidine 0.5mcg/kg bolus + 0.2mcg/kg/hr N=12
2	N=4	dexmedetomidine 0.5mcg/kg bolus[a] + 0.5mcg/kg/hr N=12
3	N=4	dexmedetomidine 0.5mcg/kg bolus[a] + 0.7mcg/kg/hr N=12
a. Study drug bolus is not required if the participant has already been receiving continuous dexmedetomidine for >12 hours		

- Minimization of bias: Randomization will occur by individual and investigators will be blinded to study/treatment arm within each cohort. The statistical analysis will account for center effects, participant characteristics (including post-surgical state and PCPC > 3), and changes over time to

minimize bias. In addition, PIs and study coordinators will undergo training to standardize assessment procedures.

- Multi-site
- Planned interim PK analysis (refer to details in **Section 9.4.6, Planned Interim Analysis)**
- Planned safety assessment by DSMB after each dose cohort

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The randomized, double blind placebo controlled trial will allow rigorous assessment of the opioid sparing effects of dexmedetomidine at various doses in the maintenance of sedation in this critically ill population.

4.3 JUSTIFICATION FOR DOSE

All recommended dosing and titration are within the range of recommended dosing for critically ill children. Fentanyl will be dosed per standard of care with no protocolized guidelines with the exception of a maximum dose. We will suggest a maximum fentanyl dose to be 5mcg/kg/hr or 250mcg/hr .

Dexmedetomidine is not approved for use in children; however, dosing recommendations include 0.5-1mcg/kg over 10-20 minutes for bolus dosing and 0.2 to 0.7mcg/kg/hr for maintenance of procedural sedation. In the pediatric intensive care unit, administration of dexmedetomidine up to doses of 2.5mcg/kg/hr have been used (dailymed) [31]. According to prior studies, the therapeutic and safe range of dexmedetomidine concentrations is 0.5 to 8 ng/ml [32].

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the trial if he or she has completed all phases of the trial, as shown in the schedule of activities, Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age is ≥ 35 weeks post menstrual age to <18 years of age at the time of enrollment.
2. Require sedation to maintain mechanical ventilation per clinical judgment.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Previous participation in this study.
2. Planned receipt of sedatives other than fentanyl or dexmedetomidine.
3. Known contraindication to the receipt of fentanyl or dexmedetomidine

4. Anticipated receipt of neuromuscular blockade for >48 consecutive hours during the study period.
5. Anticipated ventilator requirement of < 24 hours
6. Receipt of fentanyl or dexmedetomidine via continuous infusion for >48 hours immediately prior to enrollment.
7. Extracorporeal life support (including extracorporeal membrane oxygenation, ventricular assist device, etc.) at the time of enrollment.
8. Chronic use of or recent overdose of serotonergic agents (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase (MAO) inhibitors, cyclic antidepressants)
9. Known pregnancy
10. Known liver dysfunction, defined as: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2x the upper limit of normal for age
11. Known or impending renal failure defined as: anuria ≥12 hours prior to enrollment or requiring renal replacement therapy
12. High risk children, defined as:
    a. Known heart block
    b. Known bradyarrhythmia including clinically significant bradycardia (defined as requiring chronotropic agents or cardiac pacing to treat)

Note: receipt of drugs other than fentanyl or dexmedetomidine for intubation, and receipt of neuromuscular blockage for intubation, will not be considered exclusionary criteria.

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

A separate detailed recruitment and retention plan will be included in the manual of procedures (MOP). General strategies to support recruitment will include:

- Randomizing a total of 48 participants under the age of 18.
- Screening patients in the intensive care unit to determine eligibility.
- Recording participant sex, race, and ethnicity and monitoring regularly to ensure equitable enrollment.
- Identifying potential participants by executing clinic workflow alerts via their local electronic health record system, and other notification tools at strategic points of patient care.
- Incorporating study-specific decision tools for the participants, clinicians, and family enhancing transparency and confidence during the informed consent process to ensure the participant experiences a well-informed consenting process

Follow-up data at 28 days after start of study drug or ICU discharge will be collected from electronic health records eliminating the need for participant retention resources. Retention efforts will focus on

resources targeting care providers and other stakeholders critical to enrollment to maintain study awareness, continuous support and adequate communication throughout the recruitment and enrollment process.

Site identification: It is anticipated that approximately 20 sites will be needed to achieve the expected enrollment for this study. Site identification will consist of multiple activities to determine availability, accessibility, and capability to successfully recruit participants to the trial. A thorough review of each site's ability to screen and enroll participants will be conducted prior to site selection. In addition, potential sites will be screened using a feasibility survey to ensure that:

- both fentanyl and dexmedetomidine are standard of care at their institutions
- they have the appropriate population that would qualify for the study
- the site has an IDS pharmacy capable of preparing and blinding the randomized dexmedetomidine treatment arms

Protocol and study procedure training will be targeted at the participating sites, and will include webinars to cover all aspects of the study conduct; site and participant materials to assist with screening and protocol conduct; strategies to ensure consent is properly obtained from participants' parents and/or guardians; and tactics to foster follow-up compliance. Subsequent training opportunities will address questions that arise once enrollment begins (web trainings will also be recorded and posted on the website for later access to address questions or supplement training of new staff). A detailed Manual of Procedures (MOP) will be provided to each site. Site-specific working guidelines may be created to supplement the MOP. Periodic study coordinator teleconferences will be held to allow sharing of best practices. There will be a regular distribution of recruitment reports.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study will randomize participants to receive placebo (fentanyl standard of care (SOC)) titrated to sedation + saline placebo (bolus+infusion) or one of the following 3 Dexmedetomidine treatment arms in a sequential cohort fashion:

- **Cohort 1:** Fentanyl SOC titrated to sedation + Dexmedetomidine (0.5mcg/kg bolus load + 0.2mcg/kg/hr infusion)
- **Cohort 2:** Fentanyl SOC titrated to sedation + Dexmedetomidine (0.5mcg/kg bolus load + 0.5mcg/kg/hr infusion)
- **Cohort 3:** Fentanyl SOC titrated to sedation + Dexmedetomidine (0.5mcg/kg bolus load + 0.7mcg/kg/hr infusion)

COHORT	PLACEBO (N=12)	Dexmedetomidine (N=36)
1	N=4	dexmedetomidine 0.5mcg/kg bolus + 0.2mcg/kg/hr N=12
2	N=4	dexmedetomidine 0.5mcg/kg bolus + 0.5mcg/kg/hr N=12
3	N=4	dexmedetomidine 0.5mcg/kg bolus + 0.7mcg/kg/hr N=12

- The number of Infants < 1 year of age enrolled in each cohort will be determined by the DSMB and documented in a letter which will be submitted to the IRB.
- Children with neurologic compromise (defined as pediatric cerebral performance category (PCPC) > 3 or having sustained severe traumatic brain injury as etiology for their critical illness) requiring mechanical ventilator support and sedation will be restricted to no more than 8 participants per cohort.
- If the maximum dose of fentanyl is reached without obtaining adequate sedation (SBS -1 or lower, RASS score -1 or lower), participants should be provided rescue medication at the provider's discretion and should move to the follow-up phase of the study. Maximum dose of fentanyl will be defined as 5 mcg/kg/hr or 250 mcg/hr.

6.1.1.1 FENTANYL

The fentanyl can be dosed at the physician's discretion to achieve adequate sedation (responsive to light touch) per standard of care. All 4 treatment arms fall within treatment and dosing strategies that are considered standard of care. Although the study does not dictate the overall dosing strategy of fentanyl, if the maximum dose of fentanyl is reached without obtaining adequate sedation (SBS score-1 or lower, RASS score -1 or lower), participants should be provided rescue medication at the provider's discretion and should move to the follow-up phase of the study. Maximum dose of fentanyl will be defined as: 5mcg/kg/hr or 250mcg/hr. Details regarding indications and potential effects of this drug are listed below:

Fentanyl is labeled in children 2 years and up for the following indications:

- Analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
- Use as a narcotic analgesic supplement in general or regional anesthesia.
- Administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
- Use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

Fentanyl may cause some, all or none of the following side-effects.
More likely:

- Sleepiness
- Nausea or vomiting
- Constipation
- Difficult urination
- Slower heart beat

- Lower blood pressure
- Dry mouth

Less Likely
- Seizures
- Seeing, hearing, or feeling things that are not there
- Pounding in the ears
- Trembling or shaking of the hands or feet

6.1.1.2 DEXMEDETOMIDINE

Dexmedetomidine is labeled in non-intubated adults for sedation prior to and/or during surgical and other procedures. The doses proposed in each dexmedetomidine arm are within the recommendations of 0.2 to 0.7mcg/kg/hr for maintenance of procedural sedation.

Dexmedetomidine may cause some, all or none of the following side-effects.
More likely
- Lower heart rate
- Lower blood pressure
- Higher blood pressure
- Sleepiness

Less Likely
- Confusion
- Nausea or vomiting
- Dry mouth
- fever

6.1.2 DOSING AND ADMINISTRATION

The blinded and randomized infusion arms will be comprised of a placebo arm and 3 dexmedetomidine arms, each with a different dose. The dexmedetomidine arms will be initiated with a bolus dose of 0.5 mcg/kg over 10-20 minutes and an infusion rate of 0.2mcg/kg/hr, or 0.5mcg/kg/hr, or 0.7mcg/kg/hour in sequential dose escalating cohorts. Specific details for mixing the drugs to achieve identical blinded infusion rates will be included in the MOP. The blinded infusions will continue for 7 days unless extubated or discontinued sooner.

For purposes of this protocol, fentanyl should be titrated to achieve these goal parameters:
Responsive to light touch: SBS -1, RASS -1

Rescue drug: For participants who fail to achieve the targeted level of sedation or analgesia with maximum doses of fentanyl (5mcg/kg/hr or 250mcg/hr), rescue medication should be given. The choice of drug is at the discretion of the treating provider. All sedatives and analgesics administered as rescue drug (see **section 6.5 concomitant medications**) should be documented on the eCRF. ECRFs will collect dosing and timing of each dose.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Drugs will supplied by each local pharmacy as an off-the-shelf, commercially available formulation. Each site's Investigational Drug Service (IDS) pharmacy will be responsible for preparing and blinding the dexmedetomidine or placebo infusion.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Both study drugs are being provided as marketed product. Fentanyl will be administered open label to study participants. Dexmedetomidine or placebo infusion will be randomized and administered blinded to the study participants.

6.2.3 PRODUCT STORAGE AND STABILITY

Study drugs should be stored per package inserts and local standards.

6.2.4 PREPARATION

Study drugs should be prepared per local standards. Description on the blinding procedures will be provided in the Manual of Procedures (MOP).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization to treatment group will occur by individual participant. Randomization will assist in distribution of participants and their characteristics into the four groups and help minimize bias associated with treatment assignment during clinical care. Blinding will help to minimize detection and performance bias and reduce the risk of overestimated treatment effects.

6.4 STUDY INTERVENTION COMPLIANCE

Each dose of fentanyl administered to study participants during the study period will be documented in the eCRF. Study monitoring will include verification of the recorded values against documentation in the medical record. The IDS pharmacy at each site responsible for preparing the randomized and blinded dexmedetomidine or placebo infusions will maintain a record of each prepared infusion. The eCRF will record the date and time of the blinded study drug administration and the site will remain blinded until the database is locked at the conclusion of the trial.

6.5 CONCOMITANT THERAPY

Participants may continue standard therapy for existing acute or chronic medical conditions. Every effort should be made to avoid prescribing other sedatives or analgesics during the 7 day study period, unless needed for rescue in the event that fentanyl fails to be effective at a maximal dose. If the treating physician decides the participant needs additional sedatives and analgesics during the study period, administration of these drugs should be recorded on the eCRF. Therapy for existing acute or chronic medical conditions that also have sedating or analgesic properties should also be recorded. Details regarding sedatives and analgesics of interest are noted in the APPENDIX.

6.5.1 RESCUE MEDICINE

Guidelines for the provision of rescue medication are incorporated into the guidelines for dosing of the study drugs (see section 6.1.2). Administration of rescue medications should be recorded on the eCRF.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from fentanyl or dexmedetomidine arms does not mean discontinuation from the study, and remaining study procedures, including AE monitoring should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

An investigator may discontinue study intervention for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention or initiation of neuromuscular blockade, renal replacement therapy, or Extracorporeal membrane oxygenation (ECMO)
- Multiple doses of additional rescue medications are required to achieve adequate sedation

The data to be collected following study intervention discontinuation through the short term follow-up period, will include the following:

- Elimination phase PK sampling (collected within 12 hours of study drug discontinuation), if possible
- Rescue medication administration, including withdrawal medications of interest (if applicable)
- WAT-1 scores (WAT-1 score is not required if additional sedation is needed at the time of study drug discontinuation)
- Adverse events
- Safety events of special interest

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Participants whose parents or legal guardians signed the informed consent form and are randomized and do not receive the study intervention may be replaced. Participants whose parents or legal guardians signed the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, may also be replaced.

7.3 LOST TO FOLLOW-UP

Lost to follow-up will not be an option for this study because short-term follow up coincides with discharge from ICU or 28 days from start of study medication, whichever occurs first.

8 STUDY ASSESSMENTS AND PROCEDURES

Assessments and procedures will be performed at the time points indicated below.

8.1 ASSESSMENTS

8.1.1 SCREENING (DAYS -7 TO 0)

Research staff will screen potential participants for eligibility requirements, per local institutional policies. Research staff will identify potential participants by review of the local pediatric ICU census. Consent can be obtained up to 7 days prior to administration of study drug.

After the parent or legal guardian has signed the IRB-approved informed consent form/HIPAA authorization documents, and after it has been determined that the participant satisfies all inclusion and no exclusion criteria, the following evaluations and procedures will take place and should be recorded on the data worksheet or directly into the EDC at the screening visit:

1) Participant demographics, including gender, date of birth, age, race.
2) Inclusion/exclusion criteria determination as described in sections 5.1 and 5.2.
3) Pertinent medical history, including history of genetic abnormality, known congenital cardiac disease.
4) Pertinent details of clinical course until the time of enrollment, including indication for mechanical ventilation, reason for intensive care unit admission, presence of shock, seizures, or significant inflammatory state (i.e. sepsis, rheumatologic abnormality).

8.1.2 BASELINE/TREATMENT PERIOD (UP TO DAY 7)

The baseline visit can occur up to 7 days after the screening visit. It can also occur on the same day as screening. The following evaluations and procedures will take place and should be recorded on the CRF at baseline:

1) New pertinent medical history not recorded at the screening visit.
2) Physical examination – should be targeted to include participant height, weight.
3) History of TBI or PCPC status > 3
4) Post-operative status (yes/no) and operation performed.
5) Baseline FLACC, SBS, RASS, and CAPD scores for the 24 hours prior to enrollment– please record values closest to study drug initiation.
6) Mode of ventilation support at enrollment (e.g. high frequency> conventional) and settings (PIP, PEEP, FiO2).
7) Review and record any adverse events as described in section 8.2
8) Record results of laboratory studies obtained per standard of care, please record values closest to study drug initiation.

a. Specific labs values to record include: WBC count, ESR, CRP, creatinine, BUN, albumin, AST, ALT, serum electrolytes (Na, K, Cl, HCO3).

The following assessments will be conducted each day during the study period after the participant receives the initial study drug.

1) Date, time, method (bolus versus infusion), and dosing of fentanyl administration. Include dosing of fentanyl usage up to 48 hours prior to enrollment.
2) Date and time of blinded study therapy administration.
3) Concomitant medications of interest (See **Appendix**), this should include the dosing of dexmedetomidine usage up to 48 hours prior to enrollment.
4) Biological specimen collection: for drug-level analysis (including date/time of sample collection). (See **section 8.1.3 Biologic Sample Collection**).
5) FLACC, SBS, RASS, and CAPD scores, recorded at least twice daily, preferably close (+/- 1 hour) to blood sample collection for drug-level analysis. Date and time of all assessments should be recorded.
6) Review and record any adverse events as described in section 8.2.
7) Review and record safety events of special interest (see section 8.2.8 Safety Events of Special Interests), including hypotension, bradycardia, urinary retention.

Data elements that are not explicitly listed above, but are related to the respective categories of data, may be added to the study without this protocol requiring resubmission for approval by the IRB. This includes administrative changes and corrections to data definitions. Addition of data elements that represent a new area of data collection or that carry incremental human subjects protection risks will be submitted as a protocol revision requiring IRB approval.

8.1.3 BIOLOGIC SAMPLE COLLECTION: PK SAMPLING

Blood (maximum 0.5 mL/sample), up to 2 samples per day will be drawn during the 7-day intervention period. Because PK for purposes of this protocol is optimally determined after change in fentanyl dose (i.e., initiation of infusion, administration of bolus dose, or change in infusion rate), Tables 1 and 2 identify time windows from which the provider may choose to collect 2 samples each day. For example, if the participant has had an increase in fentanyl dosing per standard of care to 3mcg/kg/hr without a bolus dose, the provider could choose to obtain a sample at any 2 of the sampling options listed in Table 2. A maximum of 14 samples will be drawn during the 7 day intervention period. **Every effort should be made to collect samples in conjunction with clinical labs within the specified time periods.**

Table 1. Fentanyl bolus alone, bolus and infusion, or changing infusion rate

Sampling option	Sample time relative to bolus dose or change in infusion rate with bolus dose
1	**0-10 minutes after****
2	**30 minutes-1 hour after****
3	**2-3 hours after****
4	**4-6 hours after****
5	**8-10 hours after****

****sampling should occur after flush for bolus dosing**

Table 2. Fentanyl continuous infusion

Sampling option	Sample time relative to initiation of infusion or change in infusion rate without bolus dose
1	**2-4 hours after**
2	**18-20 hours after**
3	**24-30 hours after**
4	**32-48 hours after**

8.1.4 SHORT-TERM FOLLOW-UP (UP TO DAY 28 [+/- 1 DAY] OR DISCHARGE FROM THE ICU [+/-1 DAY])

Includes 28 days after start of study drug or discharge from the ICU, whichever occurs first. Short-term assessments are listed below and should occur daily for seven days (study days 8 through 14 or sooner if extubated or study drug discontinued prior to a full 7 day treatment period), then on day 21 (+/-1 days) and day 28 (+/- 1 days) unless discharged from the ICU sooner. Withdrawal drug dosing, AE, and ESI assessments should occur at approximately 0800 and should document the current clinical state and any drug administration for the prior 24 hour time period. WAT-1 assessments should occur twice daily, approximately 12 hours apart.

1) Administration (yes/no) and total daily dose (per kg) in the prior 24 hour time period of the following drugs of interest if initiated during the hospitalization with the intent to prevent/treat withdrawal: lorazepam, diazepam, methadone, oxycodone, or clonidine.
2) Record WAT-1 scores twice a day.
3) Review and record any AEs as described in section 8.2.
4) Review and record safety events of special interest daily (see section 8.2.8 Safety Events of Special Interests), including hypotension, bradycardia, urinary retention.

On day 28 (+/-1day) or discharge from the ICU, the following details of clinical course should also be captured if not previously documented.

1) Date of extubation
2) Date of ICU discharge

8.2 UNANTICIPATED PROBLEMS, ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document/electronic consent; and (b) the characteristics of the participant population being studied;

- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2.2 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.2.3 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2.4 CLASSIFICATION OF AN ADVERSE EVENT

8.2.4.1 SEVERITY OF EVENT

For adverse events (AEs) the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.4.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to

concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.4.3 EXPECTEDNESS

The Site PI or designee will be responsible for determining whether an adverse event (AE) is serious and/or drug related. Site PIs or designees will be provided standard risk information from the drug label for reference as part of the study materials. Any AE that is considered Serious and Drug-Related will be sent to the Safety Surveillance team at Johns Hopkins University where expectedness will be determined on behalf of the sponsor. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention and drug label. Events that are mentioned in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation, are considered unexpected. Details of the Safety Surveillance process will be captured in the Safety Management Plan.

Alternatively, due to the fact that the targeted study population is critically ill, requiring mechanical ventilatory support, any events that are consistent with the underlying illness (which may include clinical deterioration and potentially death) will be considered expected. These events will be determined by the site PI or designee as disease related events, and not AE. These events will be recorded in the CRF and will be reviewed by the DSMB during interim analyses.

8.2.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The Site PI or designee will record all reportable events (Unanticipated problems, both non serious AE and SAEs and events of special interest) with start dates occurring any time after initial study drug administration throughout the timeframe of study participation, up to 28 days or until discharge from the ICU (whichever occurs first). Events will be followed for outcome information until resolution or stabilization.

8.2.6 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the

following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB within 7 days of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

The study's clinically responsible individual will complete a Serious Adverse Event in the data system within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Safety within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be submitted to safety within 24 hours of site awareness.

All SAEs will be followed until resolution or stabilization. Additional information about SAE reporting can be found in section 8.2.8.

8.2.7 ADVERSE EVENT REPORTING

AEs will be entered in the data system within 7 days of identification. Further details will be included in the MOP.

As participants in this study may have pre-existing medical conditions and will be currently hospitalized, those pre-existing conditions will not be considered as adverse events unless they worsen or increase in frequency or intensity after administration of study drug. New events that occur or the worsening in frequency or intensity of pre-existing conditions will be reported as adverse events or, if serious reporting criteria are met, serious adverse events.

8.2.8 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol, investigator brochure, or product label and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. SAEs related to study procedures (sample collection, assessments) will be entered in the data system within 24 hours of identification.

Serious adverse events that do *not* qualify as a study drug-related adverse event for the DOSE trial and should not be reported are:

- Medical or surgical procedures (e.g. surgery, transfusion); however, the condition that required the procedure is considered a study drug-related adverse event if the situation developed or worsened due to study drug administration
- Pre-existing diseases or baseline conditions present or detected before the start of study drug that do not worsen in frequency or intensity due to study drug administration.
- Any events considered to be related to recovery or typical post-operative course

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

8.2.9 EVENTS OF SPECIAL INTEREST

The following events of special interest will be evaluated and recorded on the CRF.

Table 3: Events of Special Interest

Events of special interest	Definition
Hypotension	Decrease in systolic or mean arterial blood pressure requiring any of the following interventions: fluid administration, decrease or discontinuation of study drug, or inotrope or pressor initiation or increase in dose
Bradycardia	Clinically significant decrease in heart rate defined as requiring a decrease in dose or discontinuation of the study drug, initiation of atropine or other chronotropic agent, or need for cardiac pacing
Urinary retention	Need for urethral catheterization

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary

- Mean hourly dose of fentanyl in mcg/kg/hr during the period of blinded study drug administration

Secondary

- Sedation based on SBS, RASS scales relative to fentanyl and dexmetetomidine plasma concentrations (Cmax, Cmin,Css) and area under the concentration time curve (AUC)
- Incidence of SAEs, and safety events of special interest including clinically significant episodes of hypotension, bradycardia, urinary retention

Exploratory

- Average, maximum, and minimum daily CAPD scores
- Average, maximum, and minimum daily WAT-1 scores; Use of alternative analgesics for withdrawal.

9.2 SAMPLE SIZE DETERMINATION

Assuming a mean daily dose of fentanyl of 96mcg/kg in the control group, and a mean daily dose of 72mcg/kg in the experimental group, and a standard deviation of 24mcg/kg in daily fentanyl administration, the sample size of N=48 children randomized to fentanyl + placebo vs. fentanyl + dexmedetomidine (any dosing cohort) provides at least 80% power to detect a 25% decrease in total daily fentanyl dose (in mcg/kg) in children concomitantly treated with dexmedetomidine.

This sample size will also provide precision of fentanyl and dexmedetomidine population parameter estimates of elimination clearance within 60% to 140% of the geometric mean estimates, assuming a coefficient of variation of the parameter estimates as high as 80%.

In addition, the proposed sample size of 36 participants in the dexmedetomidine arms should be sufficient to describe the targeted safety events of special interest (bradycardia) with adequate precision (Wilson's confidence limits: 0.0608, 0.2866; width 0.22), assuming an event incidence of approximately 14%.(dailymed)

9.3 POPULATIONS FOR ANALYSES

Efficacy population: All participants enrolled who received at least 1 dose of fentanyl or dexmedetomidine will be included in the primary (efficacy) endpoint analysis.

PK populations: All participants enrolled with at least 1 evaluable PK sample will be included in the PK analysis.

Safety population: All participants enrolled who received at least 1 dose of fentanyl or dexmedetomidine will be included in the safety analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

As a first step in the statistical analyses of this study, we will summarize baseline demographic characteristics of participants enrolled in this study, as well as summarize the clinical characteristics and safety profile of the participant sample. This will be followed by analyses of the primary and secondary outcomes, and safety data. Finally, we will perform basic statistical analysis on the exploratory specific aims.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary outcome: Mean hourly fentanyl dose

The mean hourly dose of fentanyl (in mcg/kg/hr) during the period of blinded study drug administration will be compared between the placebo arm and the 3 combined dexmedetomidine arms. Daily doses per participant will be treated as a continuous outcome. The normality of these data will be assessed with histograms and Q-Q plots. Because each participant will have multiple, repeated measures of daily fentanyl (up to 7 days per participant), the difference in mean daily dose between the placebo arm and the combined dexmedetomidine arms will be compared using a random effects, mixed model, with random intercepts per participant, and a treatment indicator. In addition to considering the difference in mean daily fentanyl use by treatment regimen (placebo v. dexmedetomidine arms combined), we will also consider the trend of fentanyl use over the 7 days of mechanical ventilation by considering time (as continuous), treatment, and treatment by time interaction terms in the random effects regression model. In the case of non-normally distributed outcome measures, we will consider normal transformations of daily fentanyl use prior to creating the random effect regression model, as well as robust methods for estimating the standard errors of the model coefficients. Group differences in daily fentanyl use will be presented as group mean +/- 95% CI obtained from the random effects model coefficients. Adjusted analyses controlling for demographic and clinical characteristics may be performed if baseline imbalances between the treatment arms are present. No missing outcome measures will be imputed; however, multiple imputation methods will be used to estimate missing data for the covariates. The random effects model as described above is robust under the assumption of data missingness at random. Additional sensitivity analyses will be performed, whereby missing daily fentanyl doses are replaced with extreme values seen from the distribution of fentanyl doses seen in this population to determine how sensitive the model results are to non-ignorable missingness.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary outcome: Sedation score as measured by SBS and RASS scales

Secondary analyses will consider group differences in sedation scores as well as how fentanyl and dexmedetomidine plasma concentrations (Cmax, Cmin, Css, and area under the concentration time curve) are statistically associated with sedation. This secondary outcome is independent of results and findings of the analyses on the primary outcome. Both the SBS and RASS scores are ordinal scales, with the SBS ranging from +2 to -3, and the RASS ranging from +4 to -5. As with the primary outcome measure, multiple sedation scores will be obtained per participant over the 7 days of mechanical ventilation, creating a longitudinal data set with days nested within the participant. These longitudinal ordinal data will be modeled using multilevel ordered logistic analyses, which estimate the probability of a participant having a sedation score >= k, based treatment arm and adjusted for clinically important covariates The probability of a shift towards higher or lower sedation levels will be presented as an adjusted odds ratio +/- 95% CI obtained from the multilevel model coefficients.

Given the hypothesis that the amount of fentanyl and dexmedetomidine doses delivered have an impact on sedation, we will create ordinal models that regress SBS and RASS scores on administered fentanyl and dexmedetomidine doses. Administered doses of these drugs will be quantified with pharmacokinetic parameters, including Cmax, Cmin, Css and area under the concentration time curve. Results from these models will be presented as the adjusted odds of a shift in sedation (+/- 95% CI) per unit change in administered dose, with the appropriate units given by the pharmacokinetic parameters considered. It is very likely that not all pharmacokinetic parameters will be predictive of sedation, so only those that are predictive will be considered in a parsimonious ordinal model.

9.4.4 SAFETY ANALYSES

Safety Outcomes: SAEs, and safety events of special interest, including clinically significant episodes of hypotension, bradycardia, urinary retention.

The safety analyses will be performed using descriptive statistics to quantify SAEs and other safety events by placebo arm and separately by each dexmedetomidine arm. SAEs and the other safety events will also be tabulated by organ system within treatment assignment. As the study is not powered to test for non-inferiority of the safety events by dexmedetomidine exposure compared to the placebo arm of fentanyl alone, no statistical tests will be performed on group differences in the safety outcomes. SAEs will also be tabulated by the relatedness to the treatment assignment as detailed in Section 8.2.3.2.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics such as the number of observations, mean, median, 95% confidence interval, standard deviation, standard error, minimum, and maximum will be considered for continuous variables. Other descriptive statistics such as counts, proportions, and/or percentages will be presented by treatment arm to summarize discrete variables. Differences in these data will be determined between the placebo and dexmedetomidine arms combined using confirmatory analyses (e.g. t-tests, non-parametric tests, and differences in proportions). Any noted differences in the baseline demographic or clinical characteristics of the participant sample may be considered as covariates in the regression models to be used on the primary and secondary outcomes.

9.4.6 PLANNED INTERIM ANALYSES

The sample size for interim analysis is based on the ability to precisely estimate the clearance of fentanyl and dexmedetomidine in participants using population PK techniques. For both fentanyl and dexmedetomidine, we anticipate a CV% for CL of no more than 80% for each of the following age groups: 0-<2, 2 - <6, 6 - <12, and ≥12. Age groups are based on the FDA Pediatric Exclusivity Study Age Groups (CDER Data Element Number C-DRG-00909). Based on this CV%, at least 8 participants for each age group will be adequate to precisely describe the CL with a 95% CI [confidence interval] within 60% and 140% of the geometric mean[33].

A DSMB for this study will be comprised of three identified members. They will adhere to the DSMB charter and will convene prior to the first participant, after every Dexmedetomidine dose cohort, and at the completion of the study. They will review the interim PK analyses as well as any reported SAEs for the study. If there is a determination of unexpected, significant, or unacceptable risk to participants,

specifically if 3 or more study product related SAEs occur, the chair of the DSMB is authorized to halt enrollment and convene an ad hoc DSMB meeting to review.

9.4.7 SUB-GROUP ANALYSES

Treatment arm differences for both the primary and secondary outcome measures will be determined for different sub-groups of the sample. Emphasis will be placed on differences in treatment arm by sex and race/ ethnicity. Other clinically important sub-groups based on PCPC > 3 status and post-operative status will be considered. Differences in the primary and secondary outcome measures will be determined by including treatment arm by demographic variable (e.g. sex, race) terms in regression models described under Sections 9.4.2. and 9.4.3 to estimate treatment arm differences for each sub-group of demographic variable under consideration. Wald tests will be performed to test the null hypothesis that all interaction terms equal zero. Results of these analyses will be presented in a forest plot.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

The data for the trial will be presented at each day within participant, creating a 'long' data set. Data tabulated in this format will allow for the ease of creating the random effects regression models as described under Section 9.4.2.

9.4.9 EXPLORATORY ANALYSES

Exploratory Outcome 1: Average, maximum and minimum daily CAPD scores

Exploratory Outcome 2: Daily WAT-1 scores

As these exploratory outcomes are not confirmatory of the trial effectiveness, we will use basic exploratory analyses to determine summary statistics on these outcomes, including the central tendencies (e.g. means, medians), and measures of data spread, including variances, inter-quartile ranges, and minimum / maximum values. These summary statistics will be tabulated by day on ventilator and by treatment arm.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The investigator is responsible for following all federal, state, and local regulations regarding the obtainment of informed consent from all participants (e.g. 21 CFR 50). The investigator or designee must explain to each participant (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail.

The informed consent form(s) must be submitted by the investigator for IRB/IEC approval. The Coordinating Center will supply template informed consent forms, which comply with regulatory requirements, and are appropriate for the study. Any changes to the template consent form suggested by the Investigator must be agreed to by the Coordinating Center before submission to the IRB/IEC, and a copy of the IRB approved version must be provided to the Coordinating Center.

Due to restrictions on the number of visitors allowed at certain hospitals due to COVID-19, an electronic Consent form will be made available for parents or legal guardians to sign remotely, if needed. The electronic consent will be approved by the IRB and provided to the sites as an option for consenting participants in the study.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant's legal guardian will be asked to read and review the document. The legal guardian will sign the informed consent document prior to any procedures being done specifically for the study. A copy of the informed consent document will be given to the legal guardian for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to their legal guardian that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If an electronic consent is used, a copy of the signed electronic consent will be provided to the legal guardian.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the sponsor to investigators, funding agencies, and regulatory authorities. If the study is prematurely terminated or suspended, the site Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants/legal guardians will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants, specifically if 3 or more study product related SAEs occur, the chair of the DSMB is authorized to halt enrollment and convene an ad hoc DSMB meeting to review
- Demonstration of efficacy that would warrant stopping
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, DSMB, and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Utah, Utah Trial Innovation Center, Data Coordinating Center. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study data will be de-identified and archived at the University of Utah Trial Innovation Center, Data Coordinating Center.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Kanecia Zimmerman, MD, MPH	Sapna R. Kudchadkar, MD, PhD Associate Professor Anesthesiology & Critical Care Medicine, Pediatrics, and Physical Medicine & Rehabilitation
Duke Clinical Research Institute Duke University Medical Center	Johns Hopkins University Charlotte Bloomberg Children's Center
Durham, NC	Baltimore, MD
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This study will be overseen by a network of investigators from the Trial Innovation Network at Duke University, Vanderbilt University, Johns Hopkins University and the University of Utah (Utah Trial Innovation Center, Data Coordinating Center), all sponsored by the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health. Trial leadership will include an Executive Committee consisting of investigators at the above institutions and personnel with operational expertise. A Data Safety Monitoring Board (DSMB) will monitor the safety of the trial. The Manual of Operations (MOP) will include a list of study team roles and responsibilities of those involved in the conduct, management, or oversight of the trial.

10.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including pediatric clinical pharmacology, pediatric critical care, pediatric sedation, and drug safety and efficacy. Members of the DSMB will be independent from the study conduct and free of conflict of interest, and measures will be in place to minimize perceived conflict of interest. The DSMB will meet prior to the initiation of the study and for an interim PK analysis assessment. The DSMB will assess safety data after each dosing cohort. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NCATS and the Executive Committee.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the Duke Clinical Research Institute.
- A combination of on-site and centralized monitoring will be employed to conduct a risk-based approach to monitoring. This will include verification of a percentages of key eCRF variables and data sources as well as indicators of protocol adherence. Remote monitoring activities, using a variety of data completeness/ timeliness/quality reports will be conducted by the site management and monitoring team. The actual number of on-site visits will be determined by the data quality noted in the remote monitoring reports and any concerns as to protocol adherence raised by the site management team. In addition, monitors may provide in-service training, review site processes, and address questions from the site investigators and coordinators as needed. Details of the monitoring activities and timelines for report distribution will be included in the Clinical Monitoring Plan. Due to the small sample size and anticipated short duration of this study, no independent site audits are planned.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The University of Utah Trial Innovation Center will develop an electronic data capture (EDC) system that will permit data entry from clinical sites in a secure manner. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Worksheets from the EDC will be provided to sites to facilitate collection and/or abstraction of data at each clinical site. Selected worksheets will require investigator or research coordinator signatures, and will be maintained at the clinical site for inspection by site monitors and as part of record retention for the study.

The University of Utah will develop a detailed workflow for data collection, including definitions of data elements and training materials for the clinical sites. Utah will also provide remote data quality monitoring via the EDC and the Utah discrepancy management system. Sites are expected to complete data entry within 7 days of clinical events, and are expected to resolve data queries (discrepancies) within 7 days of notification. Discrepancy aging reports will be provided to study leadership and will be visible to all participating clinical sites and funding agencies.

Data collection forms that are used at clinical sites must be secured under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

10.1.8.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years from the date of Federal Financial Report (FFR) submission. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed prior to that time without the written consent of the sponsor.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1

- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, either reported to the Utah Data Coordinating Center through the EDC or in the monitoring reports, depending upon the mechanism through which the deviations were noted. Protocol deviations may require reporting to the funding agency, DSMB, or IRB. Such reporting should be undertaken at the instruction of the Utah Data Coordinating Center or the study executive leadership. Further details about the handling of protocol deviations will be included in the MOP.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

A public use dataset will be created by the Utah Data Coordinating Center and made available within 24 months of the last participant related procedure in the study. The dataset will be published in a manner consistent with policies of the NIH.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership, in conjunction with the National Center for Advancing Translational Sciences, has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CAPD	Cornell Assessment of Pediatric Delirium
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
FLACC	Face, Legs, Activity, Cry, Consolability Scale
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCATS	National Center for Advancing Translational Sciences
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RASS	Richmond Agitation and Sedation Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBS	State Behavioral Scale
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
WAT-1	Withdrawal Assessment Tool-1

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APPENDIX 1

CONCOMITANT MEDICATIONS

Anesthetics

Local

Bupivacaine
Lidocaine
Ropivacaine

Inhaled

Desflurane
Isoflurane
Nitrous Oxide
Sevoflurane

Benzodiazepines

Alprazolam
Clonazepam
Diazepam
Midazolam
Lorazepam

Barbiturates

Pentobarbital
Phenobarbital

Opiates

Buprenorphine
Codeine
Fentanyl
Methadone
Morphine (all formulations)
Oxycodone (all formulations)
Oxymorphone
Remifentanil
Hydromorphone

Paralytics

Cisatricurium
Rocuronium
Succinylcholine
Vecuronium

Other sedatives

Ketamine
Propofol
Clonidine
Diphenhydramine

Chloral hydrate
Dexmedetomidine

Monoamine Oxidase Inhibitors
Phenelzine
Selegiline
Tranylcypromine

Inhibitors and inducers of CYP3A4, CYP2B6, or CYP2C9
Itraconazole
Ketoconazole
Verapamil
Sertraline
Phencyclidine
Thiopental
Ticlopidine
Phenobarbital
Rifampicin