Measuring Opioid Tolerance Induced by Fentanyl (or Other Opioids) (MOTIF Study) CPCCRN Protocol Number 026

Collaborative Pediatric Critical Care Research Network
Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD)

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This protocol is CPCCRN Protocol Number 026, and the lead CPCCRN investigator for this protocol is K.J.S. (Sunny) Anand, MBBS, D.Phil., Arkansas Children's Hospital.

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PROTOCOL TITLE:

Measuring Opioid Tolerance Induced by Fentanyl (or Other Opioids)

Short Title: MOTIF Study
CPCCRN Protocol Number: 026

Lead Investigator and Author:
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Arkansas Children's Hospital

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Abstract

Following admission to a Pediatric ICU (PICU), critically ill children requiring mechanical ventilation and invasive monitoring receive opioids for analgesia and sedation.[1, 2] Therapeutic goals for the use of analgesic and sedative drugs are to reduce pain, anxiety, or agitation, allow mechanical ventilation, prevent physiological stress responses and avoid secondary complications.[3] PICU patients receive opioid therapy routinely, often leading to opioid tolerance[4, 5] and dependence.[6–9] These occur more commonly in infants and children, because of developmental changes in metabolism, excretion or dose/response curves, receptor subtypes, signal transduction, receptor induction, and regulatory pathways. Advances in opioid pharmacology cannot be applied to critically ill children because the incidence and risk factors for opioid tolerance in PICU patients remain unknown. We propose a prospective, observational study of 450 patients to describe the incidence and identify risk factors for opioid tolerance in ventilated children receiving opioid analgesia. The primary endpoint is defined by a doubling of the total daily opioid dose from initiation of opioid therapy; secondary endpoints include alternative measures of opioid tolerance. Data on opioid use, concomitant therapies, demographic and explanatory variables will be collected for the duration of opioid therapy, or 14 days after enrollment, until PICU discharge or the patients death. Rates of opioid tolerance will be summarized as proportions achieving tolerance by 7 and 14 days after initiation of opioids. We will also seek evidence for clinical variables that elevate the risk for opioid tolerance in mechanically ventilated children. Waiver of informed consent will be requested because the studys scientific validity requires 100% accrual of eligible patients.

1 Study Summary

1.1 Hypothesis

The hypothesis of this prospective, observational study is that opioid tolerance occurs frequently in PICU patients, particularly those receiving ≥ 4 days of continuous fentanyl or morphine infusions.

1.2 Specific Aims

Specific Aim 1. To describe the incidence of opioid tolerance in ventilated infants and children receiving fentanyl or morphine infusions in the PICU.

Specific Aim 2. To seek evidence of and describe the risk factors associated with development of opioid tolerance in the PICU.

1.3 Primary Endpoint

The primary endpoint for the MOTIF Study is the incidence of opioid tolerance among PICU patients receiving morphine or fentanyl infusions for analgesia and sedation. For the purposes of this study, opioid tolerance is defined by a doubling of the total daily opioid dose from the initiation of opioid therapy (0-24 hours) in the PICU.

1.4 Secondary Endpoints

Secondary endpoints for the MOTIF study are:

1. Average daily fentanyl or morphine dose within age groups (μg/kg/day, all opioid drugs will be normalized to fentanyl equivalent doses using well-established opioid conversion ratios);

2. Peak fentanyl or morphine infusion rate (μg/kg/hour, again all opioid drugs will be normalized to fentanyl equivalent doses using published opioid conversion ratios);

3. Total cumulative dose (mg/kg) and duration of fentanyl or morphine exposure (hours) during the stay, measured from the time of the first dose given after PICU admission and until study exit.

1.5 Explanatory Variables

These include demographic and clinical variables (such as age, gender, history of prior exposure, age at first exposure, duration of opioid therapy, use of concomitant medications, etc.) in order to identify possible risk factors for development of opioid tolerance during PICU therapy, and to generate hypotheses for future studies. In addition, since some opioid drugs are highly lipophilic (e.g. fentanyl) and others are not (e.g. morphine), we will calculate BMI and ideal body weight to evaluate the impact of increasing obesity on opioid tolerance.

1.6 Patient Eligibility

1.6.1 Inclusion Criteria

Critically ill children admitted to the PICU are eligible for enrollment if they are:

- between 37 weeks post-conceptional age and less than 18 years; AND
- receiving ventilatory assistance through an endotracheal tube or a tracheostomy; AND
- receiving fentanyl or morphine infusion for analgesia or sedation.

1.6.2 Exclusion Criteria

Children are ineligible to be enrolled as study subjects if ANY of the following is true or anticipated:

- are premature and have not reached the post-conceptional age of 37 weeks, OR
- have a history of drug abuse or alcohol dependence, OR
- for patients less than 3 months old, if the mother has a history of drug abuse during this pregnancy, OR
- are on ECMO or are likely to be placed on ECMO support within 24 hours after PICU admission, OR
- are receiving continuous infusions (of any drugs) for nerve blocks, plexus blocks, or epidural anesthesia, OR
- are receiving opioid therapy via patient-controlled analgesia (PCA) pumps, OR
- were receiving regularly scheduled opioid therapy for more than one week before admission to the PICU, OR
- previously enrolled in this study, OR
- lack of commitment to aggressive intensive care therapies.

1.7 Anticipated Recruitment and Study Duration

We propose enrollment of 450 subjects, a sample size that will permit estimation of the incidence of opioid tolerance with a precision of 4 to 5%. This sample will provide 80% power to detect outcome differences of 14% or higher in exploratory comparisons between subgroups of approximately equal size. The accrual period is anticipated to be between four and 12 months.

1.8 Human Subjects

Waiver of informed consent will be requested for this study because the scientific validity of the study, to determine the true incidence of opioid tolerance among patients admitted to the PICU requires 100% of eligible patients over the study interval. The study fulfills regulatory requirements for a waiver, because there are no changes in clinical practice, no therapeutic interventions, only minimal risk to the patient (loss of privacy), and obtaining informed consent would threaten the scientific validity of the study.

2 Background and Significance

As more and more children survive critical illness and injury, the population of children with special needs is expanding, and the number of children needing pediatric intensive care unit (PICU) admission is concomitantly growing.[10] Advances in monitoring and interventions for hemodynamic instability, airway and ventilator technology, innovative imaging, pediatric general and microsurgical techniques, and the emerging knowledge of the pathophysiology of organ failure are among the developments underlying the remarkable decline in mortality from conditions that were uniformly fatal in the past.[11–15]

While the decline in mortality and scientific understanding of the pathophysiological basis of pediatric critical care practice are positive developments for children, the consequences of repeated exposure to the environment and interventions of intensive care are of concern to parents, developmental scientists, pediatric generalists and subspecialists,[16–21] as well as the larger scientific community.[22–24] Recurrent or prolonged exposure to analgesic and sedation regimens and agents may lead to the induction of drug tolerance and dependence in children with prolonged exposure to these drugs.[6–9] The unique pharmacology of opioids and other sedative or analgesic agents in infants and children is impacted in a manner that is complex

and understudied. The developmental trajectory might be expected to effect changes in metabolism, excretion and dose response curves for these drugs.[25–28] At critical developmental windows, pediatric patients express unique receptor subtypes (e.g. opioid, glutamate, or serotonin receptors), signal transduction mechanisms, receptor induction, and regulatory pathways that are distinctive from adults.[29–36]

2.1 Critically Ill Children Routinely Receive Opioid Analgesia

Analgesic regimens for children admitted to the PICU commonly include opioids because of their efficacy in reducing the stress of critical illness, acute pain, postoperative pain, inflammatory pain, and cancer pain.[1] PICU patients receive routine opioid therapy via continuous infusions, potentially facilitating the development of opioid tolerance[4, 5] and dependence.[7]

In addition to analgesia, sedation is commonly used to alleviate anxiety, agitation, fear, and the risk of accidental extubation, or dislodgement of catheters, drains and monitoring equipment.[37–42]

The synergy between commonly used analgesic and sedative agents is well known.[41, 43] There is a paucity of evidence from well-designed randomized controlled trials or prospective cohort studies investigating the safety, efficacy, and clinical utility of analgesic/sedative drugs in pediatric patients.[44, 45] Investigating the efficacy of analgesia or sedation in critically ill children is also logistically difficult, because of the current lack of validated, sensitive or specific methods for the assessment of analgesia/sedation across all pediatric age groups,[37, 46–48] different developmental stages, and in children with disability.

2.2 Variability in Current Sedation and Analgesic Strategies in Contemporary PICUs

Surveys of analgesia and sedation practices from PICUs in various developed countries have demonstrated a wide variability in clinical practices.[39, 40, 42, 44, 49, 50] The use of several drug classes, innumerable agents, huge variation in the doses, frequency, and routes of administration, off-label use of designer drugs approved for adults, various drug combinations or drug rotation regimens occurs routinely[37, 39–42, 44, 50–53] — often driven by the whims and preferences of individual practitioners. Thus, it is difficult to define best practices, develop guidelines, or to move forward with scientific efforts to elucidate the key questions that might inform practice in this area. Randomized clinical

trials in this population await definitive descriptive work that would inform their design.[50, 51, 54]

Despite these difficulties, consensus guidelines for sedation and analgesia and neuromuscular blockade in PICU patients were recently published using a modified Delphi technique, while highlighting the paucity of high-quality evidence and calling for more randomized trials in this area.[45, 55] A recent prospective study, however, reported considerable variations in clinical practice.[44] Among the 338 critically ill children studied, 24 sedative and analgesic agents were used, more than 30% of ventilated patients received neuromuscular blockade, and 7.4% required physical restraints.[44] A survey of sedation and analgesia practices in the CPCCRN similarly revealed a huge variability in clinical practice, with the use of many different agents, drug classes, and drug combinations in ventilated and non-ventilated patients (unpublished data, 2007). Observational studies to determine any associations between clinical practices and patient outcomes are necessary for generating hypotheses that can be tested formally. Only after the variables in care have been identified and the outcomes of interest (e.g. opioid tolerance) have been defined would it be possible to proceed with randomized clinical trials.

2.3 Epidemiology of Opioid Tolerance in PICU Patients

Clinical studies of neonates born to heroin-addicted or methadone-maintained mothers were previously extrapolated to the iatrogenic opioid tolerance caused by prolonged opioid therapy.[5, 9] Iatrogenic opioid tolerance in young children was first reported from a retrospective chart review in neonates undergoing ECMO,[56] with 5-fold increases in the fentanyl infusion rate and increases in plasma fentanyl concentrations over 8 days of therapy.[56, 57] Opioid withdrawal symptoms occurred following a total fentanyl dose of >1.6 mg/kg or fentanyl infusions for longer than 5 days.[56, 57] Subsequent reports[58–61] suggested that opioid withdrawal occurs in 57% of PICU patients[7] and in >60% of PICUs,[62] despite careful attention to opioid weaning.[63–65] Increased complications[66, 67] and prolonged hospital stays occurred among critically ill children with opioid tolerance.[4, 68] Despite a deeper understanding of the mechanisms underlying opioid tolerance and dependence,[69] and the availability of novel therapies,[70–72] none of these advances have been applied to the care of critically ill children. This is mainly because the current prevalence of opioid tolerance in PICU patients remains unknown, and associated risk factors contributing to tolerance in PICU patients have not been described.

2.4 Clinical Significance

Practice variation primarily determined by physician or hospital preference is well described in the management of many medical conditions (e.g., bronchiolitis,[73, 74] asthma,[75] transfusion practices,[76–80] and even determination of brain death[81]). Such practice variation, based on physician preferences, is generally associated with poorer clinical outcomes[82–85] and/or higher costs,[86–88] and frequently reflects a lack of consensus regarding optimal therapy. As demonstrated by Horn and others,[73, 87–89] linking the differences in care processes with clinical outcomes is the first step in identifying best practices and thereby improving care. Guidelines to reduce practice variability are associated with improved outcomes, particularly among intensive care patients.[90–92] The American College of Critical Care Medicine developed guidelines for sedating adult ICU patients in 1995, updated in 2002,[93, 94] but similar guidelines have not been established for critically ill children. Rampant practice variation occurs in the use of opioid analgesia, often associated with complications, such as opioid tolerance and dependence. Conducting prospective observational studies to clearly define clinical outcomes and measure a baseline incidence of tolerance are important to optimize the use of opioid analgesia for critically ill children.

3 Study Hypothesis and Design

MOTIF is a prospective observational study to determine the incidence and risk factors associated with opioid tolerance in the PICU. All PICU patients treated with opioids are at risk for developing opioid tolerance, although those receiving continuous opioid infusions for ≥ 4 days are at greatest risk. A limited number of exclusions from the study population will ensure the generalization of findings to all ventilated patients in the PICU.

3.1 Hypothesis

The hypothesis of this prospective, observational study is that opioid tolerance occurs frequently in PICU patients, particularly those receiving ≥ 4 days of continuous fentanyl or morphine infusions.

3.2 Specific Aims

Specific Aim 1. To describe the incidence of opioid tolerance in ventilated infants and children receiving fentanyl or morphine infusions in the PICU.

Specific Aim 2. To seek evidence of and describe the risk factors associated with development of opioid tolerance in the PICU.

3.3 Primary Endpoint

The primary endpoint for the MOTIF Study is the incidence of opioid tolerance among PICU patients receiving morphine or fentanyl infusions for analgesia and sedation. For the purposes of this study, opioid tolerance is defined by a doubling of the total daily opioid dose from the initiation of opioid therapy (0-24 hours) in the PICU.

3.4 Secondary Endpoints

Secondary endpoints for the MOTIF study are:

1. Average daily fentanyl or morphine dose within age groups (μg/kg/day, all opioid drugs will be normalized to fentanyl equivalent doses using well-established opioid conversion ratios);

2. Peak fentanyl or morphine infusion rate (μg/kg/hour, again all opioid drugs will be normalized to fentanyl equivalent doses using published opioid conversion ratios);

3. Total cumulative dose (mg/kg) and duration of fentanyl or morphine exposure (hours) during the stay, measured from the time of the first dose given after PICU admission and until study exit.

3.5 Explanatory Variables

These include demographic and clinical variables (such as age, gender, history of prior exposure, age at first exposure, duration of opioid therapy, use of concomitant medications, etc.) in order to identify possible risk factors for development of opioid tolerance during PICU therapy, and to generate hypotheses for future studies. In addition, since some opioid drugs are highly lipophilic (e.g. fentanyl) and others are not (e.g. morphine), we will calculate BMI and ideal body weight to evaluate the impact of increasing obesity on opioid tolerance.

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3.6.1 Inclusion Criteria

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- are on ECMO or are likely to be placed on ECMO support within 24 hours after PICU admission, OR
- are receiving continuous infusions (of any drugs) for nerve blocks, plexus blocks, or epidural anesthesia, OR
- are receiving opioid therapy via patient-controlled analgesia (PCA) pumps, OR
- were receiving regularly scheduled opioid therapy for more than one week before admission to the PICU, OR
- previously enrolled in this study, OR
- lack of commitment to aggressive intensive care therapies.

3.7 Inclusion of Women and Minorities

The gender, ethnic and racial composition of patients enrolled in all CPCCRN studies is a function of the characteristics of patient populations at each Clinical Center selected by the National Institute for Child Health and Human Development (NICHD) to participate in the network. During this study, the Data Coordinating Center (DCC) will monitor patient accrual by race, ethnicity, and gender. If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate patient sample contains appropriate gender and minority subsets.

4 Data Management

Research data will be collected at the time of enrollment and daily data collection will continue until the last dose of opioids, or a total of 14 days after enrollment, or the patient's death or PICU discharge, whichever occurs first.

This protocol includes a detailed list of data elements to be collected, and if data elements are added or subtracted from this, a protocol amendment will be produced. However, specific choice sets for these data may be amended without being considered a change to this protocol. The choice sets that are listed in the protocol are intended to help the reader completely understand the intent of the data element and to assist implementation of the electronic data collection system by the CPCCRN DCC.

Data will be entered into an electronic data collection system to be designed and implemented by the CPCCRN DCC. The Study Coordinator may choose to print hard copy forms to use as worksheets. If used, the paper worksheets should be retained at the clinical center in a locked file cabinet within a locked office until the study is complete and all CPCCRN publications associated with MOTIF have been accomplished.

4.1 Definitions

Analgesia: the reduction or absence of the sense of pain without loss of consciousness, as reported by the patient, or judged clinically from the patients behavior or physiological responses

Sedation: a pharmacologically produced depressed level of consciousness associated with reduced anxiety, stress, and excitement

First study day: the period from the time that the initial dose of opioid is received in the PICU up to 23:59 hours on that day

Subsequent study days: each calendar day starting at midnight (00:00 hours) and ending at 23:59 hours after the completion of the first study day (as defined above) during which the enrolled subject is an inpatient in the PICU

Ventilated day: PICU day during any part of which the child requires mechanical ventilation support greater than chronic baseline requirements (out of the hospital), provided by endotracheal tube, tracheostomy, laryngeal or face mask

Invasive procedure: Any procedure that breaks the skin barrier or mucous membrane barrier or involves the placement of a medical device (catheter, probe, electrode, drain, prosthetic, or anything else) into a body orifice or body cavity, other than momentary suctioning of the nose, mouth, endotracheal tube, or tracheostomy tube.

Opioid tolerance: the need for increasing doses of opioid drugs in order to maintain the same pharmacological effects as those seen at the initiation of therapy. For the purposes of this study, opioid tolerance is clinically defined as a doubling of the total daily opioid dose (including infusions and boluses) as compared to the total daily opioid dose required during the first 24 hours of opioid therapy, in order to maintain adequate analgesia and sedation

Regularly scheduled opioids: the subject receives opioid drugs daily, given at regularly scheduled intervals. In response to specific symptoms or signs, if the subject has received more than one opioid dose per day, on more than three days during the past week, or a total of more than six opioid doses in the past one week, then they will be considered equivalent to those receiving regularly scheduled opioids.

Chronic opioid treatment: if the subject has received scheduled regular opioids (as defined above) for more than one week, they will be classified as receiving chronic opioid treatment.

4.2 Study Entry and Day One Data Elements

The following data elements will be obtained and recorded when a patient is enrolled into the study:

1. Study Code ID
2. Clinical Center ID
3. Date of Enrollment
4. Date and Time of Admission to PICU
5. Gender
6. Race

   American Indian or Alaska Native A person having origins in any of the original peoples of North and South America, including Central America, and who maintains tribal affiliation or community attachment.

   Asian A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

   Black or African American A person having origins in any of the black racial groups of Africa.

   Native Hawaiian or Other Pacific Islander A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

   White A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

   Other (provide text) Should provide text description.

   Stated as Unknown Explicitly stated as unknown.

7. Ethnicity

   - Hispanic or Latino
   - Not Hispanic or Latino
   - Stated as Unknown

8. Date of Birth
9. Height (cm)
10. Weight (kg)

11. Admission Pediatric Risk of Mortality III (PRISM III) Score (Based on first 12 hours of PICU admission)
12. History of previous PICU admission (Yes or No)?
13. History of NICU admission (Yes or No)? If yes, duration in days.
14. History of surgical operation in previous hospitalizations (Yes or No)?
15. Primary Diagnostic Category (Select One)
    - Asthma (reactive airway disease)
    - Cancer
    - Cardiac arrest w/in 24 hours (closed chest massage)
    - Chromosomal abnormality
    - Diabetes
    - Drug overdose (e.g. ingestion, toxicity)
    - Gastroesophageal reflux
    - Cardiovascular disease - acquired
    - Cardiovascular disease - congenital
    - HIV infection
    - Hypoxic-ischemic encephalopathy of recent onset (acute, not static)
    - Medical device malfunction
    - Meningitis
    - Pneumonia / bronchiolitis
    - Seizures (includes complications of seizure therapy)
    - Sepsis
    - Shock
    - Suicide attempt (includes intentional drug overdose)
    - Transplant
    - Trauma
    - Other Diagnosis
16. Secondary Diagnostic Category (Select One)
    - Asthma (reactive airway disease)

- Cancer
- Cardiac arrest w/in 24 hours (closed chest massage)
- Chromosomal abnormality
- Diabetes
- Drug overdose (e.g. ingestion, toxicity)
- Gastroesophageal reflux
- Cardiovascular disease - acquired
- Cardiovascular disease - congenital
- HIV infection
- Hypoxic-ischemic encephalopathy of recent onset (acute, not static)
- Medical device malfunction
- Meningitis
- Pneumonia / bronchiolitis
- Seizures (includes complications of seizure therapy)
- Sepsis
- Shock
- Suicide attempt (includes intentional drug overdose)
- Transplant
- Trauma
- Other Diagnosis

17. Chronic Diagnoses (Select Multiple)

- Bronchopulmonary dysplasia (BPD)
- Cancer
- Cerebral palsy
- Chromosomal abnormality
- Congenital heart disease
- Diabetes
- HIV infection
- Hydrocephalus
- Intraventricular hemorrhage (from perinatal period)
- Mental retardation

- Meningomyelocele / spina bifida
- Short gut syndrome
- Static encephalopathy
- Transplant
- Other Diagnosis

18. Postoperative Surgical Status (Select one)
    - Not postoperative
    - Postoperative
        - Cardiac surgery
        - Neurosurgery
        - Transplant surgery
        - Trauma surgery
        - Other surgery
19. Date and time of start of mechanical ventilation via endotracheal tube or tracheostomy during current hospital admission
20. Date and time of first morphine or fentanyl dose in the PICU — this is defined as Time 0 for the baseline opioid dose
21. Total amount of morphine or fentanyl (mg/kg) given before midnight on the first study day (total amounts of drug infusions plus additional boluses of morphine or fentanyl)
22. Total amount of midazolam or lorazepam (mg/kg) given before midnight on the first study day (total amounts of drug infusions plus additional boluses of midazolam or lorazepam.
23. Other sedative (Table 1 on the following page) or analgesic (Table 2 on page 23) agents used during the first study day. If drug combinations are used, record all components of the drug combination.

4.3 Subsequent Daily Data Elements

Study Day One is the day of enrollment, beginning at the time of the first morphine or fentanyl administration in the PICU, and ending at 23:59 on that day. Each subsequent study day is defined as midnight (00:00) to 23:59. On each subsequent day (not study day one), the following data elements

Sedative Drugs and Components	
Sedative Drugs	Answer
Ketamine	Yes or No
Propofol	Yes or No
Chloral hydrate	Yes or No
Chlorpheniramine	Yes or No
Clonazepam	Yes or No
Diazepam	Yes or No
Droperidol	Yes or No
Etomidate	Yes or No
Haloperidol	Yes or No
Hydroxyzine	Yes or No
Methohexital	Yes or No
Pentobarbital	Yes or No
Phenobarbital	Yes or No
Promethazine	Yes or No
Thiopental	Yes or No
Other (specify)	Yes or No

Table 1: Sedative agents.

Analgesic Drugs and Components	
Analgesic Drugs	Answer
Dexmedetomidine	Yes or No
Acetaminophen	Yes or No
Ibuprofen	Yes or No
Acetylsalicylic acid	Yes or No
Alfentanil	Yes or No
Buprenorphine	Yes or No
Butorphanol	Yes or No
Clonidine	Yes or No
Codeine	Yes or No
Dextromethorphan	Yes or No
Hydromorphone	Yes or No
Ketorolac	Yes or No
Meperidine	Yes or No
Methadone	Yes or No
Nalbuphine	Yes or No
Oxymorphone	Yes or No
Remifentanil	Yes or No
Tramadol	Yes or No
Other (specify)	Yes or No

Table 2: Analgesic agents.

will be collected. This daily data collection will continue through Study Day 14, discontinuation of opioid therapy, death, or PICU discharge, whichever occurs earliest.

1. Date of data collection
2. Study day number (2 to 14)
3. Weight (kg) - last measured or estimated weight
4. Was morphine or fentanyl infusion weaned (decreased) in the past 24 hours? (Yes or No)
5. Was morphine or fentanyl infusion discontinued in the past 24 hours? (Yes or No)
   If yes to this question,
   (a) Was morphine or fentanyl infusion restarted in the past 24 hours? (Yes or No)
   (b) Were intermittent opioid doses started in the past 24 hours? (Yes or No)
6. Were muscle relaxants used in the past 24 hours? (Yes or No)
7. Were physical restraints used in the past 24 hours? (Yes or No)
8. Did inadvertent or unplanned dislodgement of an endotracheal tube occur in the past 24 hours? (Yes or No)
9. Did inadvertent or unplanned dislodgement of a central venous line occur in the past 24 hours? (Yes or No)
10. Did inadvertent or unplanned dislodgement of an arterial line occur in the past 24 hours? (Yes or No)
11. Did inadvertent or unplanned dislodgement of a thoracostomy tube occur in the past 24 hours? (Yes or No)
12. Did inadvertent or unplanned dislodgement of a peripheral venous line occur in the past 24 hours? (Yes or No)
13. Did inadvertent or unplanned dislodgement of a surgical drain occur in the past 24 hours? (Yes or No)

14. Did inadvertent or unplanned dislodgement of a urinary catheter occur in the past 24 hours? (Yes or No)

15. Total amount of morphine or fentanyl (mg/kg) given on this study day (total amounts of drug infusion plus additional boluses, from 00:00 to 23:59 hours)

16. Peak hourly dose of fentanyl or morphine given during the 24 hour day (μg/kg/hr)

17. If the subject is receiving midazolam by continuous IV infusion,

    - Number of hours that the midazolam drip was continued in the 24 hour day
    - Highest hourly dose (mg/kg) for midazolam given during the 24 hour day

18. If the subject is receiving intermittent lorazepam (by any route), total dose (mg/kg) given during the 24 hour day

19. Identify all other sedative (Table 1 on page 22) or analgesic (Table 2 on page 23) agents used during the first study day. If drug combinations are used, record all components of the drug combination.

20. Did the subject undergo a surgical procedure during this 24 hour period? Yes or no

21. If the subject did undergo a surgical procedure, select the category:

    - Cardiac surgery
    - Neurosurgery
    - Transplant surgery
    - Trauma surgery
    - Other surgery

22. Did the subject undergo any invasive procedures during this 24 hour period? Yes or no

23. If yes, how many procedures?

24. Did the subject have a creatinine > 1.2 during this 24 hour period? Yes or no

25. If yes, is the patient requiring dialysis or continuous renal replacement therapy? Yes or no
26. Did the subject have hepatic dysfunction associated with an INR > 2.0 during this 24 hour period? Yes or no

4.4 Study Exit Data Elements

The following data will be recorded when the patient exits the study:

1. Study day of exit from study (1 to 14)
2. Time of exit from study (hh:mm)
3. Reason for exiting study:
   (a) Reached end of study day 14
   (b) Opioid therapy was discontinued
   (c) Patient died
   (d) Patient discharged from PICU
4. If reason for study exit was PICU discharge:
   (a) Was patient on lorazepam at the time of PICU discharge? (Yes or No)
   (b) Was patient on methadone at the time of PICU discharge? (Yes or No)
   (c) Was patient on buprenorphine at the time of PICU discharge (Yes or No)
   (d) Was patient on clonidine (for prevention or treatment of opioid withdrawal) at the time of PICU discharge (Yes or No)

5 Data Analysis

5.1 Analysis of Primary Endpoint

The primary endpoint for the MOTIF Study is the incidence of opioid tolerance among PICU patients receiving morphine or fentanyl infusions for analgesia and sedation. For the purposes of this study, opioid tolerance is defined by a doubling of the total daily opioid dose from the initiation of opioid therapy (0-24 hours) in the PICU.

Tolerance can develop at any time during opioid therapy; therefore, as would be the case for an intention-to-treat analysis in a clinical trial, subjects who die or are discharged from the PICU will be included in the denominator for this endpoint, irrespective of number of days in PICU prior to death or discharge. We will examine the incidence of this endpoint 7 days and 14 days after initiation of morphine or fentanyl infusion therapy, in order to help determine appropriate parameters for future clinical trials. Rates of the primary endpoint will be summarized as proportions achieving tolerance by 7 days and by 14 days after opioid therapy initiation, together with appropriate confidence intervals.

5.2 Analysis of Secondary Endpoints

Secondary endpoints for the MOTIF study are:

1. Average daily fentanyl or morphine dose within age groups (μg/kg/day, all opioid drugs will be normalized to fentanyl equivalent doses using well-established opioid conversion ratios);

2. Peak fentanyl or morphine infusion rate (μg/kg/hour, again all opioid drugs will be normalized to fentanyl equivalent doses using published opioid conversion ratios);

3. Total cumulative dose (mg/kg) and duration of fentanyl or morphine exposure (hours) during the stay, measured from the time of the first dose given after PICU admission and until study exit.

We will examine alternative definitions of tolerance, which may become possible secondary outcomes in future trials. We will describe these continuous secondary outcomes graphically, as well as using measures appropriate to their distributions, including mean and standard deviations for data approximating a normal distribution, and medians and interquartile ranges for substantially skewed outcomes.

As for the binary primary endpoint, we will report summary statistics of these secondary endpoints according to key study variables, and perform exploratory between-subgroup comparisons. Here, t-test/ANOVA or their nonparametric analogues will be used to assess relationships between categorical and categorized factors, while correlations and scatterplots will provide further information on associations with continuous factors. Multivariable analyses to assess factors independently predictive of secondary outcomes will be performed using linear regression models when possible (if

goodness-of-fit criteria such as assessment of residual distributions indicates a satisfactory model). For excessively skewed outcomes, transformation may facilitate use of the linear regression model.

5.3 Explanatory Variables and Additional Analyses

These include demographic and clinical variables (such as age, gender, history of prior exposure, age at first exposure, duration of opioid therapy, use of concomitant medications, etc.) in order to identify possible risk factors for development of opioid tolerance during PICU therapy, and to generate hypotheses for future studies. In addition, since some opioid drugs are highly lipophilic (e.g. fentanyl) and others are not (e.g. morphine), we will calculate BMI and ideal body weight to evaluate the impact of increasing obesity on opioid tolerance.

In exploratory analyses, we will also assess rates of the primary and secondary endpoints according to other explanatory study variables. Factors examined in these analyses will include age, gender, history of prior exposure, age at first exposure, duration of opioid therapy, use of concomitant medications, and BMI. For continuous factors, categories will be defined using clinically appropriate cut-points, or quartiles of the observed data when such cut-points do not exist or are equivocal. Chi-squared tests or exact analogues will be used to compare proportions achieving the endpoint between subgroups. Logistic regression models will be used to assess factors that are independently predictive of tolerance, starting with candidate factors showing at least a weak statistical trend toward unadjusted association with the endpoint.

This study will be collecting information on other outcomes, for example, clinical status at PICU discharge and other clinical variables. The general strategy for analyses of other outcomes collected in this study will follow that specified for the primary and secondary study endpoints. Other binary or categorical outcomes such as PICU and hospital survival will be compared using chi-square tests or exact analogues. For other continuous outcome variables, summary statistics and box-plots will be used to investigate their distributions. Where indicated in order to ensure satisfaction of assumptions, we will either use transformations or non-parametric statistics.

Univariate and multivariable regression analyses as described above (logistic for binary outcome, and linear regression for continuous outcomes appropriately transformed when necessary) will be used to assess the effects of covariates such as age, gender, and race. Tolerance-related parameters, such as time to doubling of the opioid dose, may be used as predictors in

selected analyses. For outcomes recorded as integral days, such as time in PICU, we will also examine Poisson regression analyses using the SAS GENMOD procedure.

Exploratory repeated measures analyses will make use of the daily data elements collected in this study to assess patterns of opioid dosing across time, and examine factors associated with differences in such patterns. The general linear mixed model will be used for these analyses, to control for within-subject correlation of observations across time, and to appropriately model trajectories. Polynomial or spline models may be used as appropriate in these exploratory analyses to allow maximum flexibility in modeling observed patterns of dosing or response across time.

5.4 Sample Size Estimates and Effect on Analysis

A conservative estimate of 450 subjects would be expected to yield a 95% confidence interval for proportion of opioid tolerance with precision ranging from 4-5%. We would expect 80% power to detect absolute differences in outcome rates of 14% or higher in exploratory comparisons between two subgroups of about equal size. In terms of ability to fit multivariable models, assuming an outcome rate of at least 25%, we would be able to fit models with up to 10 variables or factor levels, using the common "ballpark rule" of at least 10 events per factor in a logistic regression model. These analyses will refine the design of a randomized controlled trial and provide incidence estimates that are fairly accurate, in order to assist with the sample size calculations for a proposed intervention trial. In addition, clinical factors identified by the proposed multivariable analyses that are independently predictive of the primary outcome (or secondary outcomes) can be used for stratified enrollment in future clinical trials.

6 Accrual Projections and Duration of Study

At the CPCCRN centers from 2004-2006, there were 6,838 mechanically ventilated pediatric patients who did not require ECMO in the PICU. We propose enrollment of 450 subjects, a sample size that will permit estimation of the incidence of opioid tolerance with a precision of 4 to 5%. This sample will provide 80% power to detect outcome differences of 14% or higher in exploratory comparisons between subgroups of approximately equal size. The accrual period is anticipated to be up to 12 months.

7 Site Monitoring

Site monitors may visit each site at initiation, at a frequency to be determined by the DCC and National Institute for Child Health and Human Development (NICHD). The purposes of these visits are to help assure regulatory compliance at all sites, to improve the quality of data collection and management at each site, and to provide education to site coordinators and investigators (if needed). The site monitors may be hired by the DCC via a subcontract, and monitoring reports will be sent to the DCC.

During the site monitor visit, the monitor will inspect the Essential Documents Binder at each site. This binder contains IRB documents, investigator licenses, and other required materials. The contents of the EDB are a topic included in the training for each site. The monitor will examine the IRB documents, and will verify that the IRB approval is valid for the current version of the MOTIF study protocol. The monitor will also examine subject study files.

Source verification will be done on selected data elements, as 100% source verification is extremely expensive. The DCC will prepare lists of specific data elements to be verified. These lists will remain confidential to the DCC until completion of MOTIF to prevent the site from predicting the data elements that will be inspected by the monitor.

The monitor will also discuss the study protocol and workflow with staff at the clinical site, and will try to verify that the site is maintaining an appropriate level of expertise and education in its research staff. This is a constructive goal, because when site monitors identify areas of confusion at clinical sites, the DCC will prepare additional training materials to address these specific domains.

Finally, the monitor will verify that the study protocol is being followed, and will help assure regulatory compliance at each site.

8 Remote Monitoring

The site monitoring described in Section 7 is very expensive, and will be supplemented with remote monitoring by DCC study coordinators. The DCC will prospectively identify selected data elements for remote monitoring on a quarterly basis. The selected data elements will be different for each quarter, for each site. This prospective plan will not be shared with other MOTIF investigators until the project is completed, in order that the research coordinator will not know what data will be monitored.

The study coordinators will print out the data elements from TrialDB, and will then send a request for the site to fax the source documents for those data elements to a secure fax server at the DCC. The source documents will be compared with the TrialDB data entry. Sites that have high accuracy will be monitored less frequently than sites with less ideal performance. Sites with very poor accuracy on remote monitoring may have double data entry instituted for all data entry until accuracy improves to a satisfactory level.

9 Data Security and Backup

The DCC has a dedicated, locked 720 ft^2 server room within its offices, and the building has 24 hour on-site security guards. The DCC has a state-of-the-art computer infrastructure and coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the DCC with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption.

Direct access to DCC machines is only available while physically located inside the DCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. Security is maintained with Windows 2003 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

DCC production servers running critical applications are clustered and configured for failover events. Servers are backed up through a dedicated backup server that connects across an internal Gigabyte network to a robotic tape drive. Incremental backups occur hourly Monday through Friday from 6am to 6pm. Incremental backups also are performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the server room, and full backups are taken off site on a weekly basis to a commercial storage facility.

All personnel at the DCC have signed confidentiality agreements concerning all data encountered in the DCC. All personnel involved with DCC

data systems have received Human Subjects Protection and HIPAA education.

10 Health Insurance Portability and Accountability Act (HIPAA)

The DCC computer systems adhere to requirements of HIPAA. The DCC has offered a Business Associate Agreement (BAA) to all CPCCRN sites. The BAA is not required for the research itself, but rather, for the possession of identifiable patient information and subsequent recoding into a de-identified analytical database. This latter activity is carried out on behalf of the Covered Entity (each clinical site).

11 Human Subjects

Waiver of informed consent will be requested for this study because the scientific validity of the study, to determine the true incidence of opioid tolerance among patients admitted to the PICU requires 100% of eligible patients over the study interval. The study fulfills regulatory requirements for a waiver, because there are no changes in clinical practice, no therapeutic interventions, only minimal risk to the patient (loss of privacy), and obtaining informed consent would threaten the scientific validity of the study.

All sites will obtain IRB approval, and provide documentation of such approval to the DCC, before any subject is entered into the study. All records will be kept in a locked/password protected computer. Clinical information will not be released without the written permission of the patient, except as necessary for data quality monitoring by the CPCCRN DCC, the National Institute for Child Health and Human Development (NICHD), or other governmental regulatory bodies.

This is an observational study with no intervention; adverse events that are associated with critical illness and PICU hospitalization will not be recorded in this study.

12 Record Retention

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be

anticipated to include completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

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