RESEARCH PROTOCOL

1) **Title:**
"Emergence agitation (EA) and pain scores in pediatric patients following sevoflurane anesthesia for adenoidectomy and tonsillectomy with or without adenoidectomy comparing opioid-only, analgesia with either IV or oral acetaminophen plus opioid analgesia, a multi-center double-blinded study"

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5) **Introduction/Background:** Emergence agitation, (EA), is a state of aggressive agitation that occurs temporarily during the early stages of emergence from anesthesia. Also referred to as emergence delirium, emergence agitation occurs in both adults and children; however, it has been known since 1960 that the incidence is higher in pediatric patients (9). Emergence agitation is a major source of dissatisfaction for parents, nurses, and others taking care of these children. Patients who experience EA may suffer secondary harm due to displacement of surgical dressings, removal of catheters, and disruption of surgical closure. These patients frequently require additional interventions and may have a prolonged length of stay in the post-anesthesia care unit (PACU), even after short surgical procedures.

The etiology of EA after general anesthesia with volatile anesthetics in children remains unclear. Numerous studies exist in the literature that have attempted to correlate EA with the use of a particular anesthetic agent or technique. Specifically, the newer, volatile anesthetics, sevoflurane and desflurane, have been implicated in a 20-80% increased incidence of adverse effects, including inconsolable crying, restlessness, and agitation unrelated to pain (10). However, many of these studies did not use a validated scoring system to assess emergence agitation appropriately. In 2004, the Pediatric Anesthesia Emergence Delirium (PAED) scale was validated as a measure of emergence agitation. In this validation study, the PAED scale correlated positively with the former post-operative behavior questionnaire and the scale results correlated with clinical observations. This study also showed that patients receiving newer volatile anesthetics (sevoflurane) had a higher incidence of EA compared to those receiving halothane and this correlated with clinical observations (12).

Sevoflurane is a suitable volatile anesthetic for mask induction because of its pleasant scent and lack of irritation. It offers rapid induction of anesthesia, hemodynamic stability, and fast emergence. Although, Anesthesiologists prefer these characteristics for pediatric use, EA remains a considerable side effect of this anesthetic that demands increased resources in the PACU.

Data regarding EA incidence with different analgesic modalities using sevoflurane for induction and maintenance of anesthesia in children is scarce, and results are far from uniform. The literature is ambiguous on the incidence of EA associated with the use of sevoflurane and previous studies concerning EA in children are complicated by a lack of a validated EA scale and observed time interval after wake-up from anesthesia. The conflicting results may arise from the differences of study design, the background of study patients, and study quality. Under the existence of many confounding factors regarding EA, it is hard to draw from a single study a definitive answer about whether sevoflurane results in a higher probability of EA, as well as what effect and impact the different intra-operative analgesic modalities have on EA. When considering intra-operative analgesic modalities; co-administration of acetaminophen in addition to the standard opioid analgesic, allows for improvement of pain control without change in sensorium, as this non-opioid preparation is minimally sedating. By improving pain control, while holding the type of procedure and sedation constant, we hope to demonstrate a decrease in the incidence of EA. Of additional interest is whether the rate at which acetaminophen achieves peak CSF penetration affects EA outcomes. It is known that the primary site of action of acetaminophen is within the CNS and that its pharmacodynamic effect is dependent on achieving a sufficient Plasma/CSF level. The rate of CSF penetration has been demonstrated to occur earlier, and at a greater concentration, in patients with IV administration compared to PO or PR (16). PR route of administration was excluded in this study based on observation by Anderson et al. in pediatric post-tonsillectomy patients (17). The PR plasma acetaminophen Tmax of 3 to 4 hours was not effective in achieving the threshold plasma acetaminophen level of 10 mcg/mL in the immediate post-operative phase.

In this study, we plan to compare the incidence of EA in 3 groups of pediatric patients undergoing routine adenoidectomy, or tonsillectomy with or without adenoidectomy, using sevoflurane for induction and maintenance of anesthesia. We will use a validated and standardized measurement tool, the PAED scale, to compare EA in those receiving opioid-only based analgesia, (IV fentanyl), to patients receiving multi-modal analgesia consisting of opioid plus IV acetaminophen or opioid plus PO acetaminophen.

The inclusion of adenoidectomy, or tonsillectomy with or without adenoidectomy procedures was chosen due to the known observation in clinical experience and previous studies that patients undergoing these specific ENT procedures are at higher risk for EA. In a comprehensive review of EA published in Anesthesia and Analgesia, ENT surgery was identified as a risk factor for increased incidence of EA (15). Some hypothesize that upper airway procedures may produce a sense of suffocation when patients emerge from anesthesia. It is also hypothesized that the short duration of and fast emergence from the anesthetic are contributing factors. The accurate incidence of EA in ENT patients is hard to quantify, as studies tend to report more often on patients undergoing ear procedures that are known to be of short duration. The incidence of EA reported by this research study team in its previous work, showed the incidence of EA for adenoidectomy and adenotonsillectomy surgery to be between 34.8% and 43.5% (7).

A recent study conducted a systematic literature search and showed that the addition of an NSAID, acetaminophen or combination of the two, decreased post-operative pain scores and opioid requirements in children undergoing surgery including adenotonsillectomy, (14). Recent studies have shown improved pain scores when an analgesic adjunct is administered (6). Acetaminophen is the safest and most commonly used analgesic in the US and worldwide. Acetaminophen is also the standard therapy for post-op discharge pain management in patients with routine ENT procedures. Recent studies have evaluated the benefits of adding IV acetaminophen or PO acetaminophen to current pain regimens to assess the effects of lowering post-operative pain scores and the reduction in use of rescue doses of opioids in the recovery room. It has been reported that the route of administration of acetaminophen may have an effect in the duration of analgesia in adenotonsillectomy patients (13). This particular work showed the duration of analgesic effect was longer in patients receiving rectal acetaminophen. The optimum route of administration of acetaminophen maybe unclear but is known that different routes of administration can be associated with different analgesic effects. Intravenous acetaminophen has a faster onset and more predictable pharmacodynamics than oral or rectal acetaminophen, which may present a theoretical benefit.

IV acetaminophen is approved for the management of mild to moderate pain in pediatric patients and the management of moderate to severe pain as an adjunctive to opioids in pediatric patients 2 years of age and older. It has both an onset and peak effect of 15 minutes or less, and a duration of analgesic effect between 4 and 6 hours. Dosing depends on patient weight and age, as well as the intended frequency of administration. (For all patients 2 to12 years of age, and any patient weighing less than 50 kg, the dose is 12.5 mg/kg per dose if using an every-4-hour schedule, or 15 mg/kg per dose if using an every-6-hour schedule. The maximum single dose for these patients is 15 mg/kg. The maximum daily (24-hour) dose for these patients is 75 mg/kg (8).) Acetaminophen is metabolized via glucuronidation and sulfation in the liver. In neonates and younger children, studies have shown preferential metabolism via sulfation, possibly indicating a decreased risk of hepatotoxicity because hepatotoxicity is primarily due to metabolites that arise from the glucuronidation process. There are still concerns about hepatotoxicity primarily due to the more bioavailability of the IV formulation compared to rectal and oral administrations. In addition, the IV formulation is considerably more expensive compared to either the PO or PR routes. Adverse reactions are rare for effects such as malaise, nausea, abdominal pain, rash, hypotension, and increased levels of hepatic transaminases. Studies, met-analyses, and literature reviews show that appropriate IV acetaminophen dosing compared to placebo is not associated with hepatotoxicity. In general, most cases of hepatotoxicity have been associated with doses greater than recommended and with concomitant administration of acetaminophen-containing products (4, 5).

A recent study using similar numbers of patients per group as proposed in this study, showed lower pain scores in groups receiving adjunct administration of IV acetaminophen and rectal acetaminophen especially in the first few hours of the post-operative period(1). Another study

showed no difference of multi-modal analgesia in decreasing incidence of EA in routine ear-nose-throat surgery (2) but did not use standardized PAED scale, used Versed premedication in all patients, and studied only short lasting ENT procedures (Bilateral Myringotomies and Tube Placement). Our previous leading research study by this research team, published in the European literature, showed no difference between the incidences of EA when comparing the two most commonly used volatile anesthetics, sevoflurane and desflurane. Both groups received multi-modal analgesia using opioid plus IV acetaminophen. Clinical observations from this study showed upon study termination and thus the decline in use of adjunct IV acetaminophen, the incidence of overt EA resulted in a resurgence of needed rescue treatment. This led us to suspect the improvement in pain control using adjunct IV acetaminophen may have contributed to the diminished incidence of emergence agitation/delirium (EA)(7).

6) **Objective**: The purpose of the proposed research study is to optimize postoperative outcomes in children undergoing adenoidectomy or tonsillectomy with or without adenoidectomy, by reducing EA while maintaining adequate pain management. We aim to generate knowledge regarding the impact of multi-modal analgesia in pediatric patients undergoing the above-mentioned surgeries on the incidence of EA and post-operative pain. This information will assist anesthesiologists, parents, children and surgeons when determining the most appropriate perioperative analgesia to be administered.

7) **Hypothesis:**

The Primary Hypothesis is: The incorporation of acetaminophen in addition to standard opioid analgesia in children undergoing adenoidectomy or tonsillectomy with or without adenoidectomy will result in a decreased incidence of EA. This will be evaluated using a standardized EA measurement tool, the Pediatric Anesthesia Emergence Delirium (PAED) scale [Appendix 1].

The Secondary Hypothesis is: The route of acetaminophen administration (IV vs PO), will not have an effect on post-operative EA or pain management. This will be evaluated by comparing the pain scores of patients receiving either oral acetaminophen plus opioid or IV acetaminophen plus opioid, using the FLACC score for patients 24 months of age to 4 years of age and/or sedated patients at time of assessment, Wong-Baker FACES for patients between 4 and 7 years of age and non-verbal patients, and the Numeric Pain Score for patients equal/greater than 7 years of age.

The findings of this study, which will assess common neurobehavioral and neurocognitive disturbances after anesthesia/surgery, and assessment of immediate post-operative pain in adenoidectomy or tonsillectomy with or without adenoidectomy, can serve as an investigative platform for future studies involving other types of surgery.

8) **Aims:** In order to test our hypotheses, we propose a prospective, randomized, blinded study in pediatric patients 24 months through 7 years of age, undergoing adenoidectomy or tonsillectomy with or without adenoidectomy, with two specific aims:

Specific Aim 1: To compare the incidence of EA in pediatric patients undergoing adenoidectomy or tonsillectomy with or without adenoidectomy surgery under sevoflurane anesthesia when using opioid-only based intraoperative analgesia, (IV fentanyl), versus multi-modal analgesia consisting of IV opioid plus IV acetaminophen or IV opioid plus PO acetaminophen regimen. A standardized EA measurement tool, the Pediatric Anesthesia Emergence Delirium (PAED) scale [Appendix 1] will be the used. The primary endpoint of this aim is the incidence of EA defined as PAED score >12.

Specific Aim 2: To assess the effectiveness of acetaminophen plus standard IV opioid versus standard IV opioid treatment alone on post-operative pain management using an age-appropriate validated pain scale. We will accomplish this by comparing the pain scores of patients receiving either oral acetaminophen plus IV opioid or IV acetaminophen plus IV opioid to IV opioid alone, using the FLACC Score for patients 24 months to 4 years of age and sedated patients at time of assessment, Wong-Baker FACES for patients between 4 and 7 years of age, and Numeric Pain Scores for patients equal/greater than 7 years of age. The endpoint of this aim is the average pain score during the first 60 minutes of recovery.

9) Benefits: Potential benefits of this research study include understanding patients' response to their assigned perioperative analgesic modality and the possibility of designing an analgesic plan for future surgeries or painful procedures by utilizing the knowledge gained from the research. This study may help us identify which perioperative medication regimen is more beneficial to use in children undergoing adenoidectomy or tonsillectomy with or without adenoidectomy in order to decrease agitation, provide better pain control, and decrease exposure to multiple opioid doses if an acetaminophen adjunct medication is found beneficial.

10) Place of Study:

Nemours Children's Hospital, Orlando, Florida (Primary Site)
Wolfson Children's Hospital, Jacksonville, Florida (Nemours Jacksonville Satellite Site)

11) Study Design:

a) Prospective Randomized Study
b) Study Period: October 2017-March 2018
c) Potential participants: 375 – 475 based on 20-25% of 4,459 ENT patients in 2016
d) Study Population: 50 pediatric patients in each group between 24 months through 7 years of age undergoing adenoidectomy or tonsillectomy with or without adenoidectomy
Total Number of Patients: 150
e) Based on the preliminary data based on study from Bedirli et al. in other areas of emergence delirium, we find that a 3-armed study with equal enrollment in each arm would provide sufficient power (90%) to detect an effect size of 0.3 (moderate effect) at alpha=0.05. The secondary hypothesis would require over double the effect size (0.7) at the same power (90%) to detect any differences in the delivery route. We recognize that this aim will be greatly underpowered given the expected effect size of administration route. However, the knowledge

gained from this portion of the study will provide valuable information to form the basis of a larger multi-centered trial.

12) Methods and Materials: 150 patients between the ages of 24 months through 7 years, scheduled for adenoidectomy or tonsillectomy with or without adenoidectomy, will be randomly divided into three groups of 50 patients. Each group will receive sevoflurane induction and maintenance of anesthesia. Sevoflurane, currently the most commonly used agent for inhalational induction, will be used for induction of anesthesia, as it is less irritating to the tracheobronchial tree than other volatile anesthetic agents and is considered the standard for pediatric induction anesthesia. These three groups, (study arms), are identified as follows:

Group A: multi-modal analgesia of IV fentanyl plus IV acetaminophen and oral placebo

Group B: multi-modal analgesia of IV fentanyl plus PO acetaminophen and IV placebo

Group C: single modal analgesia of IV fentanyl plus oral placebo and IV placebo

Pre-operative procedures: The Research Pharmacy will have the following standards for randomization: prior to patient surgery date; the pharmacy will assemble study kits to contain the appropriate drug products based on the 3 randomization scenarios: A. IV Tylenol and Oral Placebo, B. IV Placebo and Oral Tylenol, or C. IV Placebo and Oral Placebo. The kits will be kept in the pharmacy and identified in a blinded fashion from other study team members. On the day of surgery, (patient dosing day), blinded study team member will provide the signed study consent to pharmacist, along with the patient's weight to be used in calculating dosages of study drug. The pharmacist will then assign the patient to 1 of 3 study arms, in a random approach. Randomization will be performed by using a method based on the biased coin method using a dynamic urn technique (11). Once the study arm has been determined, a study number will be assigned and the corresponding kit will be used to prepare the study drugs by patient weight. The blinded, randomized study kit information will be kept in a locked Excel spreadsheet, with password access, only available to pharmacy team members. All study drugs will be checked and verified by a licensed pharmacist prior to dispensing to a blinded study team member.

None of the study patients will receive premedication for sedation. Premedication is not a standard treatment at Nemours Children's Hospital (NCH) as NCH allows parental presence during induction of anesthesia to facilitate the transport of the patient to the operating room and decrease separation anxiety. Wolfson Children's Hospital will allow parental presence for study patients. Parental presence is an appropriate substitute for sedation premedication. In the pre-operative area, all patients will receive a de-identified PO syrup. The syrup will be prepared by the pharmacy and will contain acetaminophen (15 mg/kg -160mg/5mL Manufacturer: Major Pharmaceuticals), for the PO acetaminophen group and placebo flavored syrup (Manufacturer: Humco, Ingredients: Sucrose 82.3%, Purified Water, Artificial Flavors, 0.1% Sodium Benzoate as a preservative, Critic Acid, FDC Red #40, and inert ingredients), for the other two groups. This approach will maintain blindness of the peri-operative staff, and patients/parents/guardians.

Intraoperative Procedures and Administration of intra-op analgesia: Before induction of anesthesia the pre-induction vital signs will be reviewed and ASA standard monitors will be applied. Standard ASA monitors include blood pressure, ECG, pulse oxymetry, etCO2 measurement, respiratory rate and temperature. Induction of anesthesia will be accomplished via inhalation of sevoflurane (8 vol%) in nitrous oxide (70%) and oxygen (30%) at a fresh gas flow of 10 Lpm. An IV will be established and propofol 2mg/Kg will be administered to facilitate endotracheal intubation. After intubation, all children will receive fentanyl (West-Ward Pharmaceuticals) 2 mcg/kg. IV Fentanyl is considered standard of care for analgesia regimen for these types of surgery. Intra-op anesthesia team will be blinded to the use of non-opioid IV analgesia and will administer a pharmacy prepared de-identified infusion (pharmacy will blind the IV formulation of acetaminophen and all pharmacy formulations will follow regulation 797 compounding standards), following intubation that will consist of 0.9% normal saline (Baxter Pharmaceuticals), placebo for control groups and IV acetaminophen (15 mg/kg, - 1000mg/100 cc Mallinckrodt Pharmaceuticals) for the IV acetaminophen group. The maximum single dose will be 750 mg with a 24-hour maximum dose not to exceed 3,750 mg in this 24-hour period. The product will infuse for 15 minutes as recommended by the manufacturer. For maintenance of anesthesia, children will receive sevoflurane (maximum of 2.0±0.2 MAC, age adjusted) with a constant fresh gas flow of 2 L/min (maximum FIO2 of 30% air mixed with oxygen), using a semi-closed circle breathing system. Ventilation will be controlled to maintain normocapnia (ET-CO2 32-38 mmHg). Additional doses of fentanyl can be administered, per anesthesiologist's discretion, in all groups by increments of 0.5 mcg/Kg IV per dose for hemodynamic response to surgical stimulation greater than 20% above baseline. Removal of the mouth gag for tonsillectomy/tonsillectomy and adenoidectomy/adenoidectomy will be defined as the end of surgery. At this point, inhalation anesthetic will be discontinued. Fresh gas flow will be increased to a minimum of 8 Lpm, 100% oxygen. Tracheal extubation will be performed when normal ventilation is achieved and cough or gag reflex is regained.

13) Inclusion/Exclusion Criteria:

Inclusion Criteria:

a) Patients who are 24 months through 7 years of age
b) Patients who weigh ≤50 kg
c) Patients who are able to take PO medications
d) Patients who are ASA Classification I and II
e) Patients who are found to be a candidate after clinical review of detailed History and Physical Exam, review of Polysomnogram or Pediatric Sleep Questionnaire
f) Patients who are scheduled for routine adenoidectomy or tonsillectomy with or without adenoidectomy not in conjunction with another invasive or diagnostic procedure
g) Patients who meet clinical indications for surgery

Exclusion Criteria:

a) Children with a history of developmental delay or psychological disorders that may be at higher risk for EA as determined by study physician after review of history and problem list in EMR
b) Patients with previous hypersensitivity to oral or intravenous acetaminophen, fentanyl or any of its components or ingredients in placebo,
c) Patients with severe hepatic impairment or severe active hepatic disease
d) Patients with previous history of Malignant Hyperthermia or susceptibility to volatile anesthetics agents like sevoflurane
e) Any patient who weighs >50 Kg.
f) Any patient that requires premedication. Versed may contribute to an increase in EA. Premedication is reserved when parental presence is not feasible or for very anxious children.
g) Patients unable to take PO (acetaminophen or placebo) will be excluded from the study.
h) Children with severe symptomatic sleep apnea that require post-operative hospitalization.
i) Severe symptomatic sleep apnea is defined as a- patients who has a pre-operative polysomnogram and a calculated Apnea-Hypoxia Index greater than 10 b- patients with high scoring in Pediatric Sleep Questionnaire (PSQ)
j) Patients with severe symptoms and findings in physical exam that require post-operative hospital admission.
k) Participant is currently participating or has within the previous 30 days, participated in another clinical trial/research study

14) Screening/Consent Process: Potential participants will be identified and receive basic

Bringing the consent form home to review, allows the family time to discuss study participation among themselves, reach out to other family members or physicians for advice. Providing this form in advance will help the participants and parents/guardians to distinguish the difference between the study consent and surgery-related consent. The research team will obtain consent the day of surgery. The potential participants will be brought to the pre-operative area two hours prior to scheduled procedure to allow ample time to review the research study consent once more and have any additional questions answered prior to signing the consent. The research team will assure that the child, (as appropriate), and parent or guardian has the capacity to understand and make a decision about their child's participation in a research study. The study investigators, (P.I.'s/Co-I.'s), study anesthesiologists, will obtain PP consent and Assent for eligible children. A signed and dated copy of all consents forms will be given to the parents.

15)14) Intraoperative Standardization and Procedures: The surgical technique will be standardized and a limited group of three surgeons per clinical site that share same surgical technique which will be agreed upon at the start of the clinical phase. This technique will consist of only Teflon blade cautery and will require no peri-tonsilar local anesthetic injection. The number of anesthesia providers involved in the study will be limited to two anesthesiologists per clinical site. The anesthesiologists involved on the clinical component of

the protocol are those who are part of the research study team. Sevoflurane will be used for induction and maintenance of anesthesia for all groups. Study participants will receive one of the three analgesia regimens per their individual randomized treatment:

1- IV fentanyl plus oral placebo and IV placebo

2- IV fentanyl plus IV acetaminophen plus oral placebo

3- IV fentanyl plus PO acetaminophen and IV placebo

16)~~15)~~ Post-Operative Standardization and Measurements: The post-operative pain management approach will be restricted to fentanyl (0.5 mcg/Kg IV/dose titrated to effect) for moderate to severe pain. Ibuprofen (10mg/Kg) PO will be ordered for mild to moderate post-op pain. Post-op recovery staff will be limited to a maximum of three trained PACU nurses per site and will use FLACC Scale for age 24 month to 4 years of age and sedated patients at time of assessment, Wong-Baker FACES for patients 4 to 7 years of age and non-verbal patients and Numeric Pain Score for patients equal/greater than 7 years of age to assess level of pain. Episodes of clinical emergence agitation/delirium (EA), will receive rescue treatment. This treatment will consist of 0.5 – 1.0 mcg/Kg IV dexmedetomidine. Our UCF psychiatry faculty will review all cases of clinical EA. This member of our team, who is an expert in EA, will assess every case to exclude organic, pharmacologic and situational causes for EA. This analysis will be conducted on a quarterly basis and will assist us in making necessary study adjustments.

Age, gender, height, weight, procedure, duration of surgery, intra-op agents used, exposure and time of discontinuation of anesthesia to extubation will be documented for each patient. A blinded PACU nurse will monitor the patient. The Post-anesthesia unit monitoring standards consist of HR, Blood Pressure, pulse-oxymetry and respiratory rate every 5 minutes times 3 and every 15 minutes thereafter until discharged from PACU. Temperature will be obtained upon arrival to unit and every hour or as needed. All patients will be evaluated for the Aldrete Score which assesses readiness for discharge from post-anesthesia care unit. The PACU nurse will record degree of agitation using the PAED scale and measure and record the pain scores using either the FLACC for patients 24 months to 4 years of age and patients who are sedated at time of assessment, Wonk-Baker FACES for patients 4 to 7 years of age and non-verbal patients and Numeric Pain Scores for patients equal/greater than 7 years of age upon admission to the PACU and every 15 minutes for approximately 1 hour after admission, or until discharge from the PACU, whichever comes first. These nurses will all be experienced in the use of PAED scale. There will be three; two-hour study training sessions at each clinical site for PACU participating nurses. PACU nurses assigned to this study will be selecting the Modified Aldrete scores (respiration, O_2saturation, consciousness, circulation, activity) and documenting adverse events (nausea, vomiting, shivering, breath-holding, excessive secretions, laryngospasm, excessive bleeding) which will be recorded. Children will be considered discharge ready with an Aldrete score ≥9, and this will be recorded as previously stated.

17)~~16)~~ Adverse Events (AE)/Data Safety Monitoring:

Oversight Responsibilities: Oversight of the trial is provided by the Principal Investigator (PI) and Co-Investigators.

Monitoring Procedures:
The investigative team assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research protocol. Study data are accessible at all times for the PI to review. The PI and co-investigators review study conduct accrual, dropouts, protocol deviations, interim results and potential protocol modifications on a monthly basis. The PI and co-investigators review AEs individually in real-time and in aggregate on a monthly basis. The research team can decide to terminate the study at any time when analyzing reports of adverse events. The possibility of adverse events is very low. The PI ensures all protocol deviations, AEs, and SAEs are reported to the sponsor (UCF or Baptist Health) IRB and FDA (under IND Safety Report 312.32) according to the applicable regulatory requirements.

There will be a mandatory progress report to UCF on July 1st, October 1st and December 15th 2017, this will be reported to all study sites.

Collection and Reporting of SAEs and AEs:
For this study, the following standard AE definitions are used:

Adverse event: Any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

Serious Adverse Event: Any AE that results in any of the following outcomes:

- Life-threatening event
- Event requiring inpatient hospitalization or prolongation of hospitalization
- Death
- Congenital anomaly
- Persistent or significant disability/incapacity
- Required intervention to prevent permanent impairment/damage

Criteria for Stopping Study due to Adverse Events:

- Any number of deaths
- After 2 non-fatal SAEs
- After any severe neurological event
- After any 3 events where there is a moderate neurologic adverse event which is alleviated with simple therapeutic treatments

AEs are graded according to the following scale:

Mild: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.

Moderate: An experience that is alleviated with simple therapeutic treatments.

Severe: An experience that requires therapeutic intervention. If overnight hospitalization is required for treatment, it becomes an SAE.

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures or treatments (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Definitely Related: The AE is clearly related to the study procedures.

AEs identified will be captured in real time as they become known. AEs that result in visits to the ED and/or outpatient clinics will be monitored at each site through their readmission-monitoring program and reported to the department of Anesthesiology by the quality and safety officer. In addition, all AEs are reported in Orlando according to the Nemours IRB AE reporting guidelines and in Jacksonville, according to the Baptist Health IRB AE guidelines.

Treatment of AEs:
In case of a symptomatic event where a severe adverse event or any SAE is noticed, the blinding can be broken by accessing a sealed envelope that contains the assigned drugs in the randomization process and appropriate treatment will be instituted. These patients will be withdrawn from the study but the clinical and research team will continue to collect safety information. This data will be included in the safety database and reported during monthly meetings. Nemours will assure that the participant receives treatment, if needed , for study-related injuries. Neither Nemours nor the study doctor has a program to pay for medical care provided to treat the injury. If the participant has health insurance, it may , or may not, pay for the cost of treatment resulting from a study-related injury. If the participant's insurance does not pay, or if the participant does not have insurance, the participant's parent/legal authorized representative may be responsible for paying for the cost of treatment. The investigator/institution will ensure that adequate medical care is provided to a research participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution will inform the subject when medical care is needed. All AE/SAEs will be followed through their resolution or until the investigator attributes the AE/SAEs to a cause other than the study drug or assesses them as chronic or stable.

Ameliorating Measures:
Episodes of clinical emergence agitation/delirium (EA), will receive rescue treatment. This treatment will consist of 0.5 – 1.0 mcg/Kg IV dexmedetomidine as previously stated.

All patients will be instructed not to start the next dose of acetaminophen until 6 hours after last administered dose. This dose correlates to the time of intra-operative IV infusion administration.
All discharged patients will receive a call within 24 hours of surgery for follow-up. In addition to standard questions, they will be asked questions regarding abnormal rashes or discoloration of the skin and other potential adverse events like nausea, vomiting, allergic reactions, itching, respiratory difficulty, shivering, excessive bleeding, unplanned Emergency Room visit, hospitalization or death.

Clinical Research Platform
Low Risk Pathway

A. Scientific Significance: This study protocol is designed to address the scientific necessity of intra-op and post-op pain management options that are most appropriate in children undergoing common surgical procedures. This protocol addresses one of the most common risks associated with anesthetics in children less than 7 years of age, emergence agitation (EA). Evidence and clinical knowledge have shown that pain and emergence agitation negatively affect children's well-being in the post-operative period. This protocol will likely yield generalizable knowledge about subjects' post-operative pain and agitation that is of vital importance for the understanding and amelioration of these two conditions.

B. Risk/Benefit Assessment: As defined by 21 CFR Subpart D the study team will follow principles of additional safeguards in children, which includes parental permission and child assent. The research team offers a study design that includes an appropriate balance of the direct benefit of a pain regimen potentially beneficial to a subject's future surgical or painful invasive procedure, while studying the indirect beneficial science of knowing which pain regimen is most affective for patients undergoing adenoidectomy or tonsillectomy with or without adenoidectomy surgery, while offering adequate pain relief with a lower incidence of adverse events including EA. As defined in our introduction, patients of the study age range and type of surgery are at highest risk for EA. When balancing the direct and indirect benefits, the investigative team feels that these benefits present an acceptably low risk that is at minimal or slightly more than minimal risk given adult testing and clinical experience and pediatric studies of this FDA-approved drug. The research team feels that the balance between anticipated direct and indirect benefits versus expressed risks is favorable.

Plan for Data Management:

- Compliance of regulatory documents as well as study data accuracy and completeness, will be monitored through an internal study team quality assurance process.
- Confidentiality throughout the trial is maintained by securing identifiable participant data in secured, limited access locations or password protected computer files on the Nemours server. Hard copy records will be stored in a protected and limited access location at each individual site.

Withdrawal Considerations:

Our research team follows the ethical principles for participating subjects, participation is voluntary. After full disclosure, the subject can withdraw at any time from participating in the research study.

1) Participants are to be withdrawn when a participant/parent/guardian does not consent to continued voluntary study participation.
2) Participants and/or parents/guardians can request withdrawal at any time during the research study. Data collected up to point of withdrawal will remain part of the study database and subject to confidentiality protections. When voluntary withdrawal is requested, the research team will honor this request immediately and completely as allowed by law. Understanding the fact that this is a one-time intervention, a withdrawal request will result in permanent study withdrawal.
3) Participants can be withdrawn from protocol if during the course of the protocol: a newly discovered clinical aspect increases the participant's risk; the participant experiences an unexpected adverse event that the research physician feels would require study withdrawal, the participant experiences any serious adverse events; or the participant no longer qualifies for research study participation.
4) All clinical study data will be maintained, per regulations, including data on participants who withdraw voluntarily or participants withdrawn by the clinical research team. All withdrawn participants will be notified of their termination. The obtained data will be recorded on the CRF and may include demographic information, vital function monitoring, drugs administered and recovery room observations including emergence agitation and pain assessment scores.
5) The research team does not plan to replace participants who withdraw.
6) Participants who withdraw prior to the interventional portion or who will not consent for follow up, will have their protected health information maintained as private and not assessed by the research team or per Nemours guidelines.
7) Follow-up: If the participant agrees with follow up after withdrawal, the follow-up may include obtaining a 24-hour post-operative call to assess side effects or adverse event during the immediate post-operative period. This post-withdrawal assessment will follow clinical guidelines and the research team members who are treating physicians must clarify their role as a clinician. Information obtained after withdrawal during follow-up proceedings will not be used for research considerations unless there is separate consent.
8) The total number of participants who complete the entire study protocol will be at least 150.

18)~~17)~~ Statistical Analysis/Outcome Measures, Sample Size Rationale: All statistical analysis will be performed in SPSS v23 (IBM Corp.). Data will be assessed for normal distribution via Kolmogorov-Smirnov test. For continuous variables, normally distributed data will be analyzed using t-test and ANOVA. Non-normal distributions will be analyzed with non-parametric methods (Mann-Whitney U). For discrete/categorical variables, Chi-squared and gamma testing will be performed as appropriate. Time-dependent data will be analyzed via ANOVA with repeated measures or Wilcoxon-Ranked Sum testing as appropriate based normal distribution testing. All testing will be performed with $\alpha=0.05$ to determine statistical significance.

Outcomes measures from this study are based upon the PAED assessment scale and pain scores. The primary hypothesis is that multi-modal analgesia reduces PAED. The secondary hypothesis postulates that there is no difference in PAED or pain scores dependent on the route of acetaminophen administration. We will assume that the data is normally distributed for the purposes of this study, and all comparisons will be made using simple ANOVA testing. This requires two separate computations of estimated sample size.

The sample size estimation is based on data from Bedirli et al.(18) which compared the effects of Tramadol (N=39) vs dexmedetomidine (Dex; N=38) in pediatric patients undergoing tonsillectomy and adenoidectomy (T&A). They found that Tramadol had an arrival EA score of 14 (3-17), while the Dex patients had an EA score of 15 (0-17). They also found an observational pain score (OPS) of 3 (2-5) for Tramadol, and 5 (3-8) for Dex; and the Ramsay sedation scores were 2 (2-2) and 4 (2-5) after 15 minutes in the PACU for Tramadol and Dex, respectively. The authors concluded that the EA and OPS were not statistically different ($p>0.05$), but that the Dex group had a higher sedation score after 15 minutes in the PACU ($p<0.05$).

Using the results from their study, the effect size on EA was 0.08; finding a difference in EA between these two drugs for a two-tailed analysis with alpha=0.05 and beta=0.2 (Power 80%) would require a total sample size of 4192. The effect size on OPS was 0.51, requiring 120 patients total to determine a difference in a two-tailed test with alpha=0.05 and bet=0.2 (Power 80%). For Sedation score, the effect size was 1.3, requiring 22 total patients for a two-tailed test at alpha=0.05 and beta=0.2 (Power 80%).

Regardless of the outcome measure, it is simple to calculate the necessary population for which this study can be done using GPower (v 3.0.10). The first aim of the study is a three-armed blinded study, which can be estimated using an ANOVA analysis for 3 groups. The plot below depicts the required total sample size (assuming equal numbers of patients in each group) for a two-tailed analysis at alpha=0.05 vs Power for various effect sizes as found in the Bedirli study. Given that our study involves two drugs which are different from each other in their analgesic effects, we estimate that an effect size of 0.3 is reasonable for a study such as this and would still provide high power (>90%) (Figure 1).

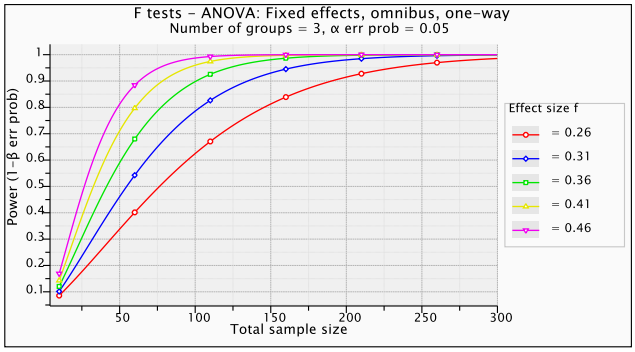

Figure 1: Plot of sample size vs study power using ANOVA fixed effects for a 3-armed study. Each curve is based upon an individual effect size.

For the secondary measure in the study, comparing the administration route of the acetaminophen, a standard t-test will be employed. The null hypothesis is that there is no difference between the administration routes. As seen in Figure 2, a two-tailed t-test for alpha=0.05 with equal numbers of patients in each group, an effect size of 0.7 would be required to achieve a study power of 90%, which indicates that a stark difference in route of administration would be required for detection at sufficient power levels to consider the difference real. A small effect (0.2) would require almost 5,000 patients, which is beyond the expectations of a single-center study.

Overall, based on the preliminary data based on study from Bedirli et al. in other areas of emergence delirium, we find that a 3-armed study with equal enrollment in each arm would provide sufficient power (90%) to detect an effect size of 0.3 (moderate effect) at alpha=0.05. The secondary hypothesis would require over double the effect size (0.7) at the same power (90%) to detect any differences in the delivery route. We recognize that this aim will be greatly underpowered given the expected effect size of administration route. However, the knowledge gained from this portion of the study will provide valuable information to form the basis of a larger multi-centered trial.

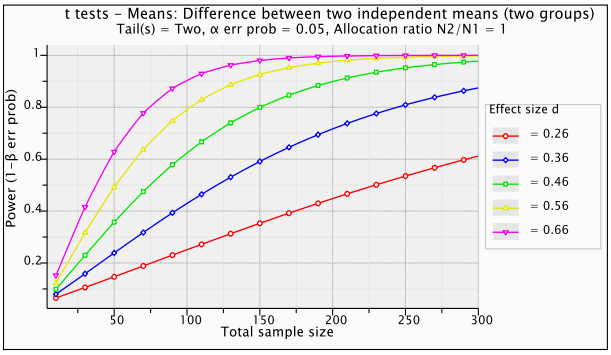

Figure 2: Plot of sample size vs study power using t-test difference for means with equal group size. Each curve is based upon an individual effect size.

19)18) References:

(1)-Paediatric Anaesthesiology 2010 Nov;20(11):1028-35.
Two-agent analgesia versus acetaminophen in children having bilateral myringotomies and tubes surgery.

Rampersad S1, Jimenez N, Bradford H, Seidel K, Lynn A.

(2)- Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen).
Drugs. 2009;69(1):101-113.
Middle East Journal of Anaesthesiogly, 2016 June; 23(5):543-8.
Comparison of the effects of preemptive intravenous and rectal acetaminophen on pain management after inguinal herniorrhaphy in children: a placebo-controlled study.

Khalili GR, Shafa A, Yousefi R.

(3)- Allegaert K, Anderson BJ, Naulaers G, et al. Intravenous paracetamol (propacetamol) pharmacokinetics in term and preterm neonates. *European Journal of Clinical Pharmacology* 2004;60(3):191-197.

(4)- Allegaert K, Rayyan M, De Rijdt T, Van Beek F, Naulaers G. Hepatic

tolerance of repeated intravenous paracetamol administration in neonates. *Paediatric Anaesthesiology* 2008;18(5):388-392.

(5)- Palmer GM, Atkins M, Anderson BJ, et al. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *British Journal of Anaesthesiology* 2008;101(4):523-530.

(6)- Tobias JD. Weak analgesics and nonsteroidal anti-inflammatory agents in the management of children with acute pain. *Pediatric Clinician* North America. 2000;47(3):527-543.

(7)- Jeremy N. DRISCOLL, Brian M. BENDER, Carlos A. ARCHILLA, Carol M. KLIM, J. HOSSAIN, George MYCHASKIW II, Julie L. WEI
Comparing incidence of emergence delirium between sevoflurane and desflurane in children following routine otolaryngology procedures, *Minerva Anestesiologica* , 2016; NOV 30

(8) Ofirmev Production Information, Mallinckrodt Pharmaceuticals, 2017 OFV 1683 02/17

(9) Smessaert A, Schehr CA, Artusio JF Jr. Observations in the immediate postanaesthesia period. II. Mode of recovery. British Journal of Anaesthesiology 1960;32:181–5.

(10) Welborn LG, Hannallah RS, Norden JM, Ruttimann UE, Callan CM. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. Anesthesia and Analgesia 1996;83:917–20.

(11) Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *The Lancet* 2002;359:515-519.

(12) Development and Psychometric Evaluation of the Pediatric Anesthesia Emergence Delirium Scale
Nancy Sikich, M.Sc., R.N.; Jerrold Lerman, B.A.Sc., M.D., F.R.C.P.C., F.A.N.Z.C.A.
Anesthesiology 5 2004, Vol.100, 1138-1145.

(13) Capici F, Ingelmo PM, Davidson A, et al. Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children. British Journal of Anaesthesiology 2008;100:251–255.

(14) Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory

drugs (NSAIDs) in children

Ivan Wong,1,2 Celia St John-Green,2 and Suellen M Walker1,3
Paediatric Anaesthesiology: 2013 Jun; 23(6): 475–495.
Published online 2013 Apr 9. doi: 10.1111/pan.12163

(15) Emergence delirium in children: many questions, few answers: Vlaikovic, GP, Sindielic, RP, Anesthesia and Analgesia 2007 Jan; 104(1):84-91

(16) Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen.

Singla NK[1], Parulan C, Samson R, Hutchinson J, Bushnell R, Beja EG, Ang RRoyal MA
Pain Practice. 2012 Sep;12(7):523-32. doi: 10.1111/j.1533-2500.2012.00556.x. Epub 2012 Apr 24.

(17) Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model.

Anderson B[1], Kanagasundarum S, Woollard G.

Anaesthesia Intensive Care. 1996 Dec;24(6):669-73.

(18) Tramadol vs dexmedetomidine for emergence agitation control in pediatric patients undergoing adenotonsillectomy with sevoflurane anesthesia: prospective randomized controlled clinical study
Nurdan Bedirli* , Mehmet Akçabay and Ulku Emik
BMC Anesthesiology (2017) 17:41
DOI 10.1186/s12871-017-0332-4

APPENDIX 1: Pediatric Anesthesia Delirium (PAED) Scale

	SCORE
1. The child makes eye contact with the caregiver. 2. The child's actions are purposeful. 3. The child is aware of his or her surroundings. ~~4.~~	**4 = Not at all** **3 = Just a little** **2 = Quite a bit** **1 = Very much** **0 = Extremely**
~~5.~~4. The child is restless. ~~6.~~5. The child is inconsolable.	**0 = Not at all** **1 = Just a little** **2 = Quite a bit** **3 = Very much** **4 = Extremely**

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CRF

Name:	**Age:**
Sex:	**MRN:**
Height:	**Weight:**
Patient #:	**BMI:**
Date:	**Group: (circle below)**
History:	**Opioid only -**
Diagnosis:	**Opioid plus IV acetaminophen-**
Operation:	**Opioid plus PO acetaminophen-**
Surgeon :	**Anesthesiologist:**

Anesthesia Induction:

Time: **MAP:** **HR:** **SpO_2:**

Hypnotic: Sevo **%**

Analgesia: Fentanyl **µg,**

IV acetaminophen **mg,**

PO acetaminophen **mg**

Postoperative analgesia:

Intubation Time :

Surgical Start Time:

Anesthesia Maintenance:

Sevo: **MAC**

Time: **MAP:** **HR:** **SpO_2:**

Time End of Surgery: **Time End of Sevo:**

Time End of Extubation: **FGF:** **L/min**

Time: **MAP:** **HR:** **SpO_2:**

PACU Record (Time: to)

	Admission to PACU	15 min	30 min	45 min	60 min			Discharge from PACU
PAED Scale								
Modified Aldrete Scores								
FLACC								
Wong-Baker FACES								
Numeric Pain Score								
Pain Meds Used (Fentanyl Dose; Ibuprofen)								

Adverse events to be documented:

Nausea

Vomiting

Shivering

Breath-holding

Respiratory depression

Pruritus

Excessive secretions

Laryngospasm

Excessive bleeding

Anaphylaxis

Skin reaction – rash

Skin reaction – discoloration including jaundice

Abdominal Pain

Hypotension

Death

Unplanned hospitalization

Other