Title:	**OPIOID-FREE VERSUS TRADITIONAL ANESTHETIC WITH OPIOIDS FOR TONSILLECTOMY – Multi-Center**
Short Title	Opioid-free Tonsillectomy
Drug Name(s):	Ketorolac and Dexmedetomidine
Regulatory Sponsor:	The Children's Hospital of Philadelphia
eIRB Number	IRB 19-016618
Protocol Date:	May 15, 2020

Amendment 1 Date: June 18, 2020

Amendment 2 Date: September 29, 2020

Amendment 3 Date: December 4, 2020

Amendment 4 Date: May 25, 2021

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OPIOID-FREE TONSILLETOMY SITE INVESTIGATORS SIGNATURE PAGE

Protocol Title	**OPIOID-FREE VERSUS TRADITIONAL ANESTHETIC WITH OPIOIDS FOR TONSILLECTOMY – Multi-Center**
Version Date	May 25, 2021
Site Principal Investigator	
Institution	

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.
Send a copy of this page to the Study Principal Investigator.

Site Principal Investigator Signature _____

Date: _____

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ABBREVIATIONS AND DEFINITIONS OF TERMS

CHOP	Children's Hospital of Philadelphia
AE	Adverse event
SAE	Severe adverse event
TCG	Traditional care group (opioid regimen)
OFG	Opioid-free group (intervention regimen)
POD	Post-operative day
NSAID	Non-steroidal anti-inflammatory drug

ABSTRACT

Context:

Over 2 million Americans have been diagnosed with an opioid use disorder (OUD), and in 2017, 47,600 overdose deaths were attributable to opioids. [1,2] In 2016, 3.6% of adolescents (age 12-17) endorsed inappropriate opioid use; this number doubled among young adults aged 18-25.[3] Single dental and perioperative opioid exposures are significantly associated with chronic opioid use among pediatric patients (4.8% exposed patients vs 0.1% non-exposed patients).[4,5] Emerging literature suggests that limited opioid exposure significantly correlates with future risk of OUD, and that procedures associated with mild to moderate post-operative pain can be managed effectively without opioids.[1,6] High-volume pediatric centers, including Seattle Children's, report equivalent outcomes after tonsillectomy with both standard opioid-containing and opioid-free regimens (see Appendix III, data from Seattle Children's opioid-free protocol).[7]

Aim:

- Primary Objective

To determine if an opioid-free anesthetic provides equivalent acute postoperative pain relief in tonsillectomy.

Study Design:

- Prospective, randomized, multi-center trial

- Setting/Participants:

  The setting including Children's Hospital of Philadelphia and The University of Tennessee Health Science Center.

  The participants will include up to 350 subjects age 2-18 undergoing tonsillectomy.

Study Interventions and Measures:

The study will be a 1:1 block randomization per site by surgical type (classic versus intracapsular) to either standard anesthetic – traditional care group (TCG) or an opioid-free (OF) intra-operative anesthetic regimen. Both groups are investigational.

Main study outcome measures are as follows:

- Baseline Questionnaire
- Acute assessment: pain & delirium scores
- POD 1 & 5 questionnaire: Bleeding, hydration, family satisfaction with patient recovery, pain medication use and (patient or parent) reported pain score
- Chart review and brief questionnaire: POD 30 for readmission and medical reattendance, including calls to physician

PROTOCOL SYNOPSIS

Study Title	**OPIOID-FREE VERSUS TRADITIONAL ANESTHETIC WITH OPIOIDS FOR TONSILLECTOMY – Multi-Center study**
Funder	CHOP (Foerderer and McCabe Fund grants)
Study Rationale	To date, an opioid-free anesthetic for tonsillectomy has not been rigorously studied in a randomized, controlled pediatric trial. If a randomized trial establishes that an opioid-free technique is equivalent, hundreds of thousands of annual pediatric opioid exposures, and subsequent risk of misuse, will be eliminated. This will also decrease post-operative opioid prescriptions, which have also been linked to widespread opioid misuse and abuse in communities.
Study Objective(s)	**Primary** To determine if an opioid-free anesthetic provides equivalent acute postoperative pain relief in tonsillectomy. **Secondary** To determine if post-operative pain at home is not significantly different with an opioid containing regimen for tonsillectomy.
Test Article(s)	Ketorolac, Dexmedetomidine
Study Design	Prospective, randomized, single-center trial study
Subject Population **Key criteria for Inclusion and Exclusion:**	**Inclusion Criteria** 1. Males or females age 2 to 18 years. 2. Girls after menarche must have a negative pregnancy test 3. ASA ≤ 3 4. Scheduled tonsillectomy or tonsillectomy combined with adenoidectomy and/or ear tube placement. 5. Parental/guardian permission and if appropriate, child assent (patient consent if age 18). **Exclusion Criteria** 1. Current (within the last 30 days) opioid use 2. Patients that took pre-operative Celebrex on the day of service 3. High risk for surgical site hemorrhage, including bleeding disorder diagnosis or poor intraoperative hemostasis 4. Multiple scheduled surgeries at the same time other than adenoidectomy and/or ear tube placement 5. History of drug abuse, chronic pain, bleeding disorder • Chronic Diseases such as Sickle Cell Disease for which treatment with opioids may be clinically indicated. 6. Significant congenital disorders, medication allergies or comorbidities, specifically a pre-disposition to bradycardia or conduction abnormalities, cyanotic cardiac disease and use of medications that would increase risk of bleeding or bradycardia. • History of hepatic dysfunction, renal dysfunction, thrombocytopenia, or anemia (including pre-surgery laboratory abnormalities)

- History of hypersensitivity to NSAIDs
- Patients with asthma, including patients who have experienced aspirin- or NSAID-sensitive asthma or a history of exacerbation when aspirin or NSAIDs are administered (e.g. bronchospasm, urticaria, etc.)
- Subjects receiving medications that could impact metabolism of either study drug should also be excluded
- Trisomy 21 diagnosis

6. Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.

7.Parents or subjects who do not speak English

8. Patients on a Ketogenic diet

*Eligibility will be confirmed on the day of surgery (e.g pregnancy testing results will not be available before then, current opioid use refers to timing of surgery). Only subjects who meet all of these criteria will complete study procedures.

Number of Subjects

550 subjects will be enrolled to produce 350 evaluable subjects.

Study Duration

Each subject's participation will last up to 30 days, with chart review lasting up to 30 days.
The entire study is expected to last about three to four years.

Study Phases

Screening
Study Treatment
Follow-Up

- Screening: identifying potential subjects and obtaining consent
- Baseline questionnaire prior to surgery
- Intervention: randomization
- Follow-up:
  - Acute Assessment: pain and delirium scores
  - Home Assessment: POD1 phone call to ask about pain, bleeding and dehydration. POD 5 and POD 30 eSurvey via REDCap. Follow-up phone calls/referrals as necessary if responses warrant follow-up. (See Appendix I)
  - Chart review: up to 30 days post-op, in addition to brief questionnaire

Efficacy Evaluations

The primary endpoint is the median pain score (calculated by a blinded validated observer in the recovery room at two time intervals) between the two cohorts.

Safety Evaluations

Dexmedetomidine and Ketorolac are currently used frequently at participating institution clinical pediatric anesthesia practice. There is no reason to suspect an increase in risk from their use together in this study in excess of the known risks associated with each medication. Subjects will also be monitored during recovery, POD1 and POD 5 and POD 30. Subjects will also be contacted on day 1 by phone call to verify that they do not have bleeding and are drinking fluids and making urine. They will receive electronic questionnaires on POD5 and POD30. If the subject indicates on the electronic survey that "yes" they are having bleeding or "no" they are not eating or making urine, a local study investigator will call them. If subjects report that they have sought care outside of participating center for complications on the POD 30 electronic survey, a local study investigator will call them. Any study related AEs will be treated per institutional standard practice and all applicable referrals will be made. Data are attached from Seattle Children's Hospital, an institution that uses ketorolac preferentially over opioids for all tonsillectomies.[7] Colleagues at Albany Children's and Emory routinely use ketorolac for tonsillectomy and are currently

studying use to reduce opioid consumption (clinicaltrials.gov).

Statistical and Analytic Plan	Non-inferiority design to detect a difference that is equal to or less than the predefined largest clinically important difference between standard care and the intervention derived from quality improvement (QI) data. Using a value of the change in pain scores that is 15% of a single standard deviation as the non-inferiority margin (derived from internal QI data), the difference on a 0-10 pain scale is also smaller than any clinically relevant change. It will require 350 patients (175 patients per treatment group) to be 90% sure that the upper limit of a one-sided 95% confidence interval will be below 0.6 if the pain score is truly not worse for the intervention group.
DATA AND SAFETY MONITORING PLAN	Local PI will be responsible for oversight of the study safety and a Data Safety and Monitoring Board (DSMB), composed of three individuals with expertise in conduct of pediatric clinical trials, has been established. We expect no more than standard clinical risks associated with tonsillectomy, which include bleeding and dehydration. The interim analysis will occur after 50 patients, 15% of the target, have been enrolled. The DSMB board will meet at this point. In addition, The DSMB will have planned semi- annual meetings to review data and a meeting may be called by any investigator or CHOP clinician to review specific concerns. The DSMB will also receive monthly reports detailing bleeding rates in the two groups. The maximum bleeding rate requiring unscheduled clinic visits or visit to the ER, has been less than 10% in any given month. If this is exceeded in a given month, this would also constitute a stopping criteria. The IRB will be immediately notified, and the study will be halted while the DSMB examines the data. If the DSMB determines that the rate increase was similar between groups and had no plausible correlation with Ketorolac or other study medications (i.e. a new surgical technique or operator), the study would be permitted to proceed.

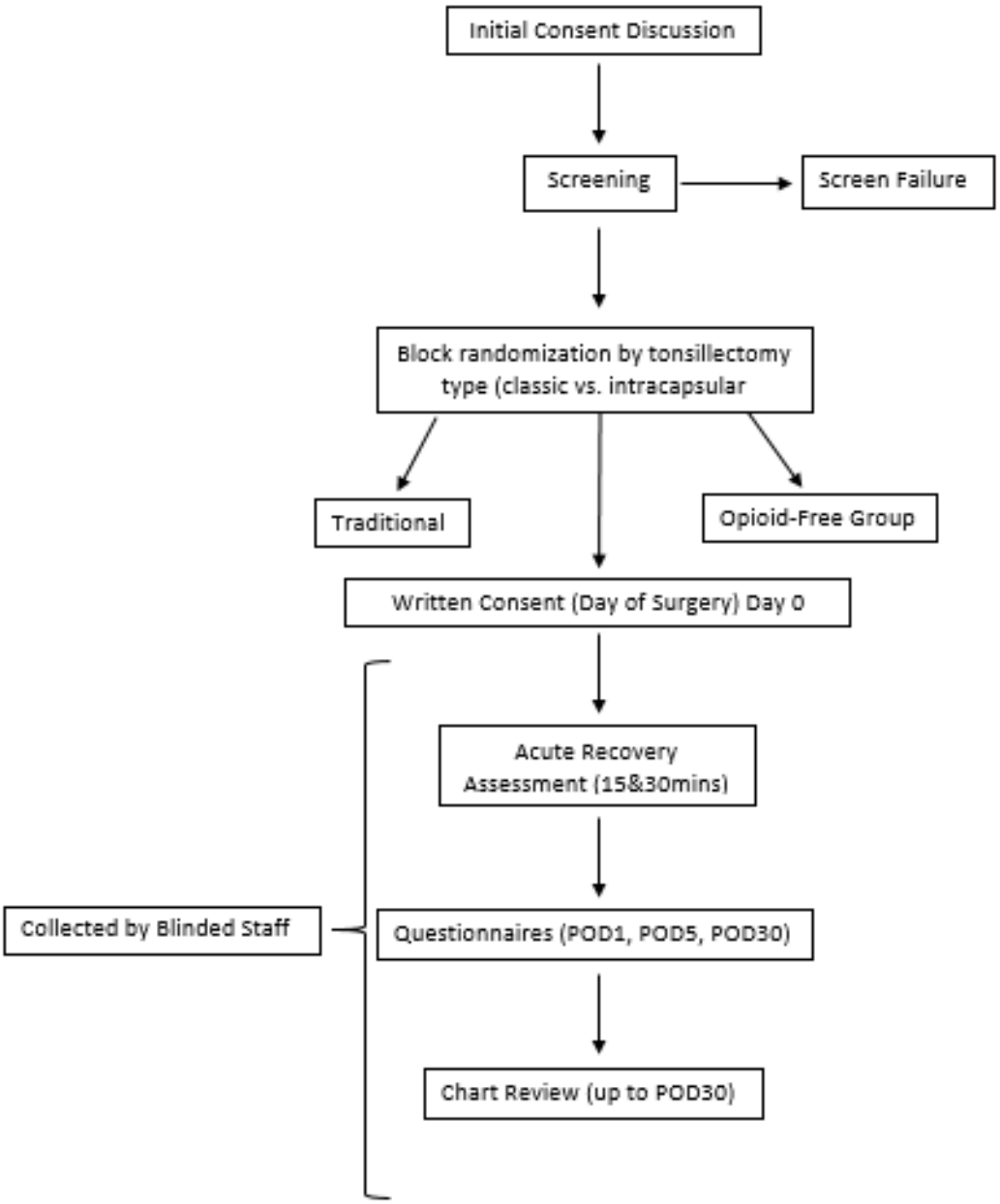
TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Surgery Recovery (minutes)**		**Follow-up**		
Study Days	**0**	**15±5**	**30±10**	**Day 1+1**	**Day 5+3**	**Day 30±3**
Informed Consent/Assent	X					
Review Inclusion/Exclusion Criteria	X					
Demographics/Medical History	X					
Prior/Concomitant Medications	X					
Randomization	X					
Pain Assessment	X	X	X	X	X	
FLACC Assessment		X	X			
Delirium Assessment		X	X			
Questionnaire	X			X	X	X
Chart Review	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X

TABLE 2: SCHEDULE OF MEDICATION TIMING

	CASE START	CASE END	RECOVERY ROOM	HOME
TRADITIONAL CARE GROUP (TCG)	Opioid/IV Acetaminophen	Opioid (if needed)	IV Opioid for severe pain; oxycodone as needed	Acetaminophen +NSAID (Opioid if needed)
OPIOID-FREE GROUP (OFG)	Dexmedetomidine/IV Acetaminophen	Ketorolac (if hemostasis verified)	IV Opioid for severe pain; oxycodone if pain still not controlled	Acetaminophen +NSAID (Opioid if needed)

FIGURE 1: STUDY DIAGRAM



Subjects from whom written consent is obtained prior to the day of surgery that are no longer found to be eligible on the day of surgery will be withdrawn from the study

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Over 2 million Americans have been diagnosed with an opioid use disorder (OUD), and in 2017, 47,600 overdose deaths were attributable to opioids. [1,2] In 2016, 3.6% of adolescents (age 12-17) endorsed inappropriate opioid use; this number doubled among young adults aged 18-25.[3] Single dental and perioperative opioid exposures are significantly associated with the development of chronic opioid abuse by pediatric patients (4.8% of exposed patients vs 0.1% of non-exposed patients).[4,5] Pediatric patients continue to receive perioperative opioids and are discharged with opioid prescriptions despite data that post-operative pain can be effectively managed without them in most cases.[1,6,8,9] For example, opioids are routinely prescribed during and after tonsillectomy, the second most common pediatric surgery (>500,000/year), despite evidence that they are associated with adverse events and recent guidelines from the American Academy of Otolaryngology that nonsteroidal anti-inflammatory drugs (NSAIDs) should be used instead with acetaminophen.[10-12] To date, an opioid-free anesthetic for tonsillectomy has not been rigorously studied in a randomized, controlled pediatric trial. If a randomized trial establishes that an opioid-free technique is equivalent, hundreds of thousands of annual pediatric opioid exposures, and subsequent risk of misuse, will be eliminated. This will also decrease post-operative opioid prescriptions, which are routine at participating centers, that have also been linked to widespread opioid misuse and abuse in communities.

If the hypotheses are correct, study results would drastically alter the standard of care. Hundreds of thousands of children would avoid opioid exposures each year, and communities will be spared from availability of excess opioids. This will not only provide evidence to adapt newer anesthetic techniques but will hopefully highlight the value of clinical effectiveness trials in pediatric anesthesia. Several pediatric hospitals report equivalent outcomes with opioid free techniques for tonsillectomy, a procedure performed on over 500,000 children each year.[7,11] However, there are no clinical effectiveness trials to support equivalent outcomes.

1.2 Description of Investigational Intervention

The study will have two groups for intra-operative anesthetic regimen. Both groups are investigational.

- Traditional Care Group (TCG): Traditional anesthetic with opioids group will receive participating center's usual clinical care for tonsillectomy, including a standardized opioid dose at the beginning of the case and again at the end if needed. Some providers also administer Acetaminophen, Dexmedetomidine and/or Ketorolac in the operating room; however, all patients receive opioids as usual care. In addition to analgesia, opioids provide sedation; dexmedetomidine is intermittently used by some providers given its sedating qualities. Dexmedetomidine will not be used intra-operatively in this cohort to prevent confounding.
- Opioid-Free Group (OFG): Opioid-Free group will receive the participating center's usual clinical care for tonsillectomy, without opioids, but including Dexmedetomidine (beginning of case), and Ketorolac (end of case after evaluation for hemostasis). This combination is used exclusively by pediatric hospitals such as Seattle Children's, given the sedating and analgesic qualities of Dexmedetomidine and the exclusive analgesic qualities of Ketorolac.

All patients will receive standard of care post-operative pain management if pain control is inadequate. If pain continues to be poorly controlled per the criteria above (FLACC ≥4 and/or provider discretion), patients will receive standard weight-based liquid Oxycodone (0.05-0.1mg/kg) which is indicated for moderate pain (FLACC≥4) at participating centers. The un-blinded PACU nurse will be encouraged to not administer oxycodone if a patient's pain is clinically controlled with non-medical interventions such as a popsicle and re-direction, which is standard of care at participating centers. The home pain

control regimen will not be altered from each surgeon's baseline protocol, which includes a NSAID (either Celecoxib or Ibuprofen), acetaminophen and a prescription for rescue opioids at the surgeon's discretion. A third group prescribes opioids and Acetaminophen only (these providers have elected to not participate in the trial).

1.3 Relevant Literature and Data

In the United States, opioid abuse is considered to have reached epidemic proportions. In 2016, 3.6% of adolescents (age 12-17) endorsed inappropriate opioid use; this number doubled among young adults aged 18-25.[3] A growing body of literature suggests that limited pediatric opioid exposure correlates strongly with future risk of OUD: even a single dental or perioperative opioid exposure has been significantly associated with chronic opioid use among pediatric patients (4.8% exposed patients vs 0.1% non-exposed patients).[4,5] Adolescents in particular are at higher risk of addiction after exposure due to changes in the reward and habit centers of the brain.[13-16] However, there is increasing evidence that procedures associated with mild to moderate post-operative pain can be managed effectively without opioids.[1,6,8] Two sites (Albany Medical and Seattle Children's) have reported equivalent outcomes with opioid-free anesthetic techniques for tonsillectomies using historical data for comparison in quality improvement initiatives at the latter institution without increased risk.[7] Post-operative analgesia was not guided by protocol but was at provider discretion. Another benefit of the OF anesthetic was a significant decrease in post-operative nausea and vomiting (PONV). However, this technique has not been rigorously evaluated in a randomized trial. A well-conducted trial that demonstrated non-inferior outcomes would contribute to a decrease in unnecessary opioid exposure.

To date, there are no pediatric clinical effectiveness trials that have addressed this question. We do know that opioid abuse is now the largest drug epidemic in American history and that pediatric perioperative exposure is significantly associated with future misuse. If this study determines that an opioid-free anesthetic is equally effective and satisfaction to patients and parents, this trial will alter the standard of care and associated risks for over a half million patients each year in the United States alone.

1.4 Compliance Statement

This study will be conducted in full accordance all applicable participating center's Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46 and the HIPAA Privacy Rule. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with participating center's IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to determine if an opioid-free anesthetic provides equivalent acute postoperative pain relief in tonsillectomy.

2.2 Secondary Objective

The secondary objective is to determine if post-operative pain at home is not significantly different with

an opioid-free regimen compared to an opioid containing regimen for tonsillectomy.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This study is a prospective, randomized, multi-centered controlled trial.

3.1.1 Screening Phase

Potential subjects will be identified from patients scheduled for elective surgery per protocol inclusion and exclusion criteria. Parental/guardian permission (informed consent) and assent when indicated will be obtained prior to any study related procedures being performed.

3.1.2 Randomization

Subject will be randomized to 1:1 intra-operative opioid-free (OFG) vs traditional care anesthetic with opioids (TCG) group per site. Randomization could occur prior to obtaining formal written consent, but will not occur until after the initial consent discussion has been completed and documented accordingly in REDCap. The treating anesthesiologist will be notified of consent status on the day of service and instructed to proceed with assigned treatment arm (emailed to them the day prior) if the patient/family has provided written consent. If the family declines on the day of service or the participant is no longer found to be eligible on the day of service, the treating anesthesiologist will be notified immediately to proceed with standard of care anesthetic treatment. Confirmation of anesthesiologist's acknowledgement of a) randomization b) consent status and c) screening confirmation on day of service will be documented in study EDC.

3.1.3 Follow-up Phase

The follow-up phase will continue for up to 30 days after surgery. Per participating center's standard clinical protocol, all patients discharged home after tonsillectomy will be contacted to assess general wellbeing and are specifically asked about hydration, bleeding and pain control. If there are any concerns, the Otolaryngology clinic is immediately called to perform a same-day assessment and to escalate care, if indicated. Please see detailed information below with regard to a patient phone call from a study clinician (nurse or doctor) on POD1 and electronic surveys on POD 5 and POD 30.

Questionnaire: Subjects will complete a baseline questionnaire after consent and prior to surgery. Subjects will be followed-up at POD 1,POD 5, and POD30. The questionnaire could be collected either over the phone or text link via REDCap to the parent's phone at the parent/legal guardian's preference. The online survey should take less than 5 minutes. The phone call should take less than 15 minutes. If families prefer to also complete the POD1 survey over the phone during the safety study follow-up call, this will be an option as well. After two attempts of calling family over the phone are unsuccessful, a text link will be sent to the family.

3.1.3.1 Chart Review

Chart will be reviewed up to POD 30 and patients will be contacted electronically to collect any complications. If subject reports bleeding, not being able to drink or make urine, a study investigator will call them.

3.2 Allocation to Treatment Groups and Blinding

The randomization sequence will be generated by statisticians by Data Coordinator Center (DCC). The randomization sequence will be maintained in study REDCap EDC by the study manager at DCC. Block randomization will be performed by surgical type (intracapsular versus classic) per site to ensure equal distribution. Randomization will occur with random block sizes of 2, 4 or 6 to ensure equal numbers of

OFG vs TCG subjects to avoid predictability of medication assignments.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The study duration per subject will be up to 30 days post-surgery, with two follow-up questionnaires at Day 1, Day 5, and Day 30. All medical records will be reviewed up to Day 30 for medical re-attendance.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at The Children's Hospital of Philadelphia (CHOP) and The University of Tennessee Health Science Center. It is expected that approximately 550 subjects will be enrolled to produce 350 evaluable subjects. Any center enrollment should be capped at 80% of total study enrollment.

3.4 Study Population

3.4.1 Inclusion Criteria

1. Males or females age 2 to 18 years.
2. Girls after menarche must have a negative pregnancy test
3. ASA ≤ 3
4. Scheduled tonsillectomy or tonsillectomy combined with adenoidectomy and/or ear tube placement.
5. Parental/guardian permission (informed consent) and if appropriate, child assent

3.4.2 Exclusion Criteria

1. Current (within the last 30 days) opioid use
2. Patients that took pre-operative Celebrex on the day of service
3. High risk for surgical site hemorrhage, determined by bleeding disorder diagnosis or evidence or poor hemostasis
4. Multiple scheduled surgeries at the same time other than adenoidectomy and/or ear tube placement
5. History of drug abuse, chronic pain, bleeding disorder
    a. Chronic disease such as sickle cell disease for which treatment with opioids may be clinically indicated
6. Significant congenital disorders, medication allergies or comorbidities, specifically a pre-disposition to bradycardia or conduction abnormalities, cyanotic cardiac disease and use of medications that would increase risk of bleeding or bradycardia.
    a. History of hepatic dysfunction, renal dysfunction, thrombocytopenia, or anemia (including pre-surgery laboratory abnormalities)
    b. History of hypersensitivity to NSAIDs
    c. Patients with asthma, including patients who have experienced aspirin- or NSAID-sensitive asthma or a history of exacerbation when aspirin or NSAIDs are administered (e.g. bronchospasm, urticaria, etc.)
    d. Subjects receiving medications that could impact metabolism of either study drug should also be excluded
    e. Trisomy 21 diagnosis
7. Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.

8. Patients on a Ketogenic diet
9. Parents or subjects who do not speak English

Eligibility will be confirmed on the day of surgery (e.g pregnancy testing results will not be available before then, current opioid use refers to timing of surgery). Only subjects who meet all of these criteria will complete study procedures. Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with participating center's IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening Visit

Below research activities will be conducted:

- Informed Consent
- Medical Record Review and data collection from standard of care
- Baseline questionnaire collection

4.2 Randomization

The study will be a 1:1 randomization to TCG or OFG Investigational Group anesthetic regimen per site level. A full summary of the intraoperative and postoperative medication doses and administration criteria are detailed in Section 7. This includes medications administered in the recovery room and medications that are prescribed to patients after discharge.

4.3 Post-Op Recovery Assessment

These study activities will be conducted 15 and 30 minutes post-op at recovery room by the blinded observer.

- Data collection as detailed in sections 5.1 and 6.3.2
- FLACC (Face, Legs, Activity, Cry, Consolability) pain assessment
- Delirium assessment

4.4 Follow up

4.4.1 Questionnaires

Questionnaires will be obtained on POD 1,POD 5, and POD 30 (See Appendix I). Patients will be also be contacted on Day 30 to verify that they did not seek care outside of the participating center's system for complications related to surgery, such as bleeding from surgical site.

4.4.2 Chart Review

A manual Chart review will be conducted up to POD 30 to assess any AE/SAEs. All AE/SAEs will be reviewed by a blinded investigator and the DSMB, if indicated.

4.5 Unscheduled Visits

The subject will be followed up daily (and more frequently, if indicated) for any study related and unanticipated adverse events until event resolution. Per participating center's standard clinical care, the post-operative protocol for patients undergoing tonsillectomy includes a phone call to assess for bleeding, pain control and adequate hydration, along with general well-being. This information is documented in local eMR and any concerns are immediately conveyed to the Otolaryngology team for follow-up.

Because Ketorolac has a terminal duration of action of 30 hours, a research staff will call the patient on POD1 to verify they have no bleeding and are drinking and making urine. Additional follow-up information will be obtained via electronic questionnaire on POD5 and POD30, including a phone call if patient reports they sought care at an outside hospital.

4.6 Concomitant Medication

All prior and concomitant pain medications used within 30 days prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Medical Record Review

The variables that will be abstracted from the medical chart:

- PHI: Name, MRN, Date of birth and event dates, email, text and phone number, and pregnancy test if applicable
- Demographics, including zip code
- Medical history, including indication for the surgery (i.e. recurrent tonsillitis, sleep disordered breathing)
- Vital Signs
- Anesthesia records
- Surgical records
- Recovery records
- Out-patient or ER records
- Pharmacy records, including history of use of opioid pain medications

5.2 Randomization

To ensure balance in treatment assignment, a block randomization approach will be applied by surgical type (intracapsular and classic). The block size will be varying (among 2, 4, 6) to avoid the predictability of assignment per site.

Randomization will be conducted through the study REDCap program by an un-blinded researcher. Randomization could occur on the day before surgery, prior to obtaining written consent. Although randomization may occur prior to having the formally signed written consent form, it will not occur until after the initial consent discussion has been completed and documented in REDCap. The assigned anesthesiologist will be emailed immediately after randomizing with the patient's assigned treatment arm. They are also cautioned that the patient has not provided written consent, yet, and they will receive another email and notified by study staff on the day of service with the consent status.

If the patient/family signs the consent form on the date of service, the treating anesthesiologist will be instructed to proceed with assigned treatment arm (arm that was emailed to them the day prior). If the family declines on the day of service or the participant is no longer found to be eligible on the day of service, the treating anesthesiologist will be notified immediately to proceed with standard of care anesthetic treatment. Confirmation of anesthesiologist's acknowledgement of a) randomization b) consent status and c) screening confirmation on day of service will be documented in study EDC.

To avoid protocol deviation or violation, randomization could only occur when all required study elements are met including re-confirmation of eligibility, surgical location and date, and research staff availability. The anesthesiologist will be notified of the anesthetic treatment group; he or she will verify that the patient is appropriate for the intervention arm by verifying that there is appropriate tonsillar bed hemostasis prior to

administering Ketorolac at the end of the case as noted in the protocol. Although not expected, any patients randomized to the OFG arm who receive intra-operative opioids will be followed per protocol and studied in a sub-group analysis. To avoid potential confounding, the surgeon will remain blinded to the patient's intervention cohort assignment.

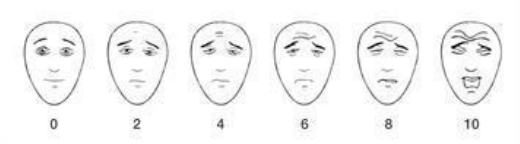
5.3 Post-op Recovery Assessment

Pain, FLACC, and delirium assessments will be conducted by a blinded study staff or clinician at 15±5 min and 30±10 min post-op after subject is awake from anesthesia.

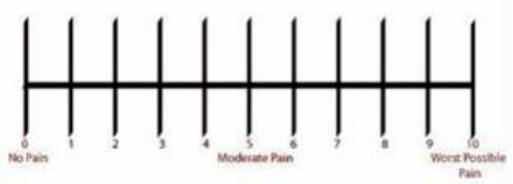
5.3.1 Pain Assessment

An age appropriate pain scale will be utilized for parent, and if appropriate, patient self-assessment of pain score at home.

Modified Bieri pain scale will be utilized if the subject is less than 10 years old.



Numeric Rating scale (NRS) 0-10 will be utilized if subject is 10 years or older.



5.3.2 FLACC (Face, Legs, Activity, Cry, Consolability) assessment

Will be used to assess pain score in the recovery room by a blinded observer.

Criteria	Score	Score 1	Score
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to,	Difficult to console or comfort

5.3.3 Delirium assessment

Delirium will be assessed with the Pediatric Anesthesia Emergence Delirium (PAED) scale.[17] We will assess delirium as it is a common confounder for pain in children emerging from anesthesia.

Point	Description of Items	Scoring				
		not at all	just a little	quite a bit	very much	extremely
1	The child makes eye contact with the caregiver	4	3	2	1	0
2	The child's actions are purposeful	4	3	2	1	0
3	The child is aware of his/her surroundings	4	3	2	1	0
4	The child is restless	0	1	2	3	4
5	The child is inconsolable	0	1	2	3	4

5.4 Questionnaire

Baseline, POD 1, POD 5 and POD 30 questionnaires will be collected. A RN or MD study team member will call the patient/family on POD1 to monitor for bleeding and dehydration. See below and Appendix I for additional information. This information will also be obtained on POD5 and POD30. Prior to discharge home, patients will be asked to record a daily maximum pain score to enter when they receive the corresponding survey. Patients will be also contacted on Day 30 to verify they did not seek care outside of the participating center for complications. The questionnaire will collect parent- and patient-reported pain scores, family satisfaction (Likert 7-point scale), and medication administration. The baseline questionnaire and a baseline pre-operative pain score, along with any recent medication use, will be assessed in the pre-operative area.

Strongly agree	Agree	More or less agree	Undecided	More or less disagree	Disagree	Strongly disagree
(1)	(2)	(3)	(4)	(5)	(6)	(7)

All questionnaires could be collected either through text message or email with a link to the online survey from REDCap, or in-person, or phone call based on the parent/legal guardian's preference. The online survey should take less than 5 minutes. The phone call should take less than 15 minutes.

Renal insufficiency and bleeding are both rare, but extremely serious complications of NSAID administration. At participating center SOC, all patients who undergo tonsillectomy receive a phone call on POD1 to assess general well-being; they are specifically asked about bleeding, swallowing, hydration and pain control. If there are any concerns, there is a well-established communication network with the Otolaryngology clinic staff, who perform a same day assessment. In the event of a serious concern, such as bleeding or risk of airway compromise, there is a system in place to arrange emergency medical transport while the patient remains on the line.

In addition to the phone call from clinical nursing staff, patients will also be contacted by research staff (research nurse or physician) on post-operative Day 1 who will ask:

1. Has your child had any bright red blood in their mouth?

2. Is your child drinking and making urine?

If bleeding or dehydration is detected, the patient will be directed to the Emergency Department for assessment (or the local hospital if closer with coordination with the surgeon's office) and the patient's surgeon will be notified for follow-up. If dehydration is detected, the patient will be directed to have their Creatinine checked. If the family is willing, the remainder of the POD1 survey will be completed at this time.

Electronic surveys that are sent on POD5 and POD30 will also ask:

1. Has your child had any bright red blood in their mouth?

2. Is your child drinking and making urine?

If subjects respond with "yes" to bleeding and/or "no" to drinking and making urine they will be called by a study RN or MD and be directed to the Emergency Department for assessment (or the local hospital if closer with coordination with the surgeon's office) and the patient's surgeon will be notified for follow-up. If dehydration is detected, the patient will be directed to have their Creatinine checked. They will also be called by one of the study MD investigators if either complication is detected. The date of a bleeding (including time of event if it occurs on POD1) or dehydration event will be captured in RedCap by the research staff.

5.5 Day 30 Chart Review

The chart will be reviewed up to 30 days after surgery to assess for medical re-attendance, including related phone calls or visits to a physician.

6 STATISTICAL CONSIDERATIONS

Statistical analysis: Based upon the quality improvement data provided by a pediatric hospital (Seattle Children's) with similar patient population demographics, we postulate that there will be no statistically significant difference between recovery room FLACC and pain scores in the two treatment groups. A non-inferiority design was specifically chosen because we are hypothesizing that there **will not be a clinically important difference** between an opioid-free anesthetic and the opioid-containing techniques (i.e.

6.1 Traditional anesthetic with opioids). [18,19]Primary Endpoint

The primary endpoint is median maximum pain score by investigational group in the recovery room, calculated by the blinded observer 15 and 30 minutes after awakening. We hypothesize that there will be no significant difference in two groups.

6.2 Secondary Endpoints

Secondary endpoints include:

- Frequency of nausea, vomiting, pruritis
- Frequency of readmission and of seeking unplanned medical attention (phone calls, office visits, ED visits)
- Frequency of non-artifactual SpO2<90% (>30 seconds)
- Percentage of patients receiving rescue opioids
- Family satisfaction with patient recovery based on seven-point Likert score
- Bleeding prevalence

6.3 Statistical Methods

6.3.1 Baseline Data

The following variables will be collected in eMR prior to surgery and after consent: age, date of surgery, surgeon years of experience (Resident, Fellow, <1 Year Attending, 1-5 Year Attending, 6-10 Year Attending, 11-15 Year Attending, >15 Year Attending), height and weight, type of tonsillectomy (i.e. intracapsular), indication for tonsillectomy, co-morbidities including history of obstructive sleep apnea (OSA), zip code, and sleep study apnea-hypoxia index (AHI) and oxygen saturation nadir values, if available. The following information will be collected from the EPIC/EMR patient record after the study encounter: dose per kilogram (kg) of all pain medications administered in the operating room, dose of all intravenous rescue opioids

administered in the recovery room and dose of oxycodone, if administered. Vital signs, including instances of sustained SpO2 <90% and persistent oxygen administration once awake secondary to desaturations will be documented in both the recovery room and inpatient setting.

6.3.2 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects randomized at Visit 1. This will be followed by a secondary protocol analysis. Data will be analyzed in SAS software version 9.4 (SAS Institute Inc., Cary, NC). Demographic characteristics and medical conditions will be presented with standard statistics: mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate, for continuous variable, and frequency and percentage for categorical variables. The balance in patients' demographical and medical characteristics between treatment groups (i.e. opioid-free group and opioid-containing standard treatment group), as well as the relationship between patients' demographical and medical characteristics with pain score, will be assessed using two-sample t-test or Wilcoxon Rank-sum test, as appropriate, for continuous variables, and Chi- square test or Fisher's exact test, as appropriate, for categorical variables, with $p<0.1$ considered indicative of unbalance or association. Normality will be assessed using histogram, the value of skewness and kurtosis. The difference between treatment (opioid-free group minus opioid-containing standard treatment group) in pain score will be presented with mean and 95% confidence interval (CI), and the upper limit of 95% CI will be compared to the prespecified non-inferiority limit (d=0.6) to assess non-inferiority. Any deviations from protocol will be assessed in a sub-group analysis that will be dependent on the variable type, as described above, and the number of deviations. To account for unbalanced variables and confounders, including a possible difference between surgical type, a multivariable linear regression will also be done. Variables that are unbalanced between treatment groups, or related to pain score in bivariate analysis will be added as covariates in the model. The primary efficacy endpoint will be the difference in pain scores between TCG and OFG groups. Secondary endpoints will include the change in side effects associated with opioid use and family satisfaction. Patients may only be enrolled and randomized after being instructed to hold their pre-operative Celecoxib. These patients will not receive any pre-operative medication, which is the same practice as the proposed second site. The post-operative medication options in the original protocol incorporate the three most common practices at CHOP: Ibuprofen and Acetaminophen (most common practice at second site), Celecoxib/Acetaminophen and Acetaminophen/Oxycodone. We will compare post-operative pain scores by surgery type, site and post-operative regimen and then only merge if no significant differences are noted for the final analysis.

6.4 Sample Size and Power

Power calculations: We therefore have powered our study to detect a difference that is equal to or less than the predefined largest clinically important difference between standard care and the intervention derived from quality improvement (QI) data. The non-inferiority margin is determined based on both statistical consideration and clinical judgement.[19] Using a value of the change in pain scores that is 15% of a single standard deviation as the non-inferiority margin (derived from QI data), 0.6 difference on a 0-10 pain scale is also smaller than any clinically relevant change. Using the cited formula, we achieved our sample size.[20] It will require 350 patients (175 patients per treatment group) to be 90% sure that the upper limit of a one-sided 95% confidence interval will be below 0.6 if the pain score is truly not worse for the intervention group.[20]

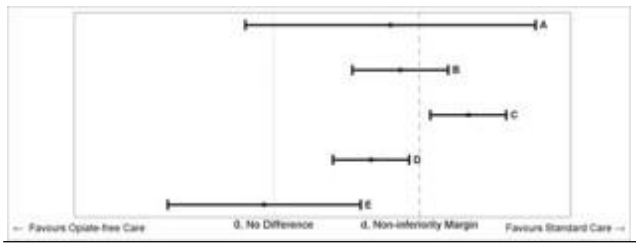


Figure. Overview of non-inferiority trial principles comparing the confidence interval (CI) of the mean difference to a predicted margin (used with permission, B. Zhang, CHOP); A,B,C: non-inferiority not demonstrated because the upper limit of CI exceeds the margin. D,E: Non-inferiority was demonstrated because the upper limit of CI did not exceed the margin

7 STUDY MEDICATION

7.1 Description

Currently providers at participating center use a combination of Opioids, Acetaminophen, Dexmedetomidine and Ketorolac for analgesia during tonsillectomy and adenoidectomy. The universal standard includes opioids

(intravenous Morphine or Fentanyl) first, followed by any combination, including all of the three other medications. It is important to note that while a few surgeons do currently permit use of Ketorolac for tonsillectomy, it is not the standard of care at participating center. Patients randomized to the intra-operative opioid- free investigational group will receive a standard inhalation induction (intravenous with Propofol at the provider's discretion), 1ug/kg of Dexmedetomidine (maximum 50ug) over ten minutes and Propofol 1- 2mg/kg if indicated following intravenous line placement, intubation with appropriate oral RAE endotracheal tube, maintenance with sevoflurane at 2.5% until in suspension with a subsequent decrease to 1.7-2%, standard doses of ondansetron (0.1mg/kg, max 4mg), dexamethasone (0.5mg/kg, max 10mg), 20 milliliters (ml/kg) of lactated ringers (LR) and ketorolac (0.5mg/kg; maximum 15mg[21]) at the end of the procedure, with extubation (awake or deep) at the provider's discretion. All patients will receive intravenous Acetaminophen prior to the conclusion of the procedure (12.5mg/kg, max 1000mg, stratified by age in the participating center formulary).

Patients randomized to the TCG investigational group will receive an identical anesthetic to the opioid-free group with two exceptions. Dexmedetomidine and Ketorolac will not be administered intra-operatively. Patients will receive the institutional standard dosing for opioids in tonsillectomy (0.5-2ug/kg fentanyl OR 0.05-0.1mg/kg morphine)

If a patient has a pain score judged as severe (current PACU standard pain evaluation -FLACC$\geq$8) based upon a consensus panel composed of anesthesiologists and nursing providers, they will receive rescue intravenous Morphine or Fentanyl per a weight-based standardized algorithm that is contained within the participating center order set "Post-op Orders." If pain continues to be poorly controlled per the criteria above, patients will receive standard weight-based liquid Oxycodone (0.05-0.1mg/kg). The un-blinded PACU nurse will be encouraged to not administer oxycodone if a patient's pain is clinically controlled with non-medical interventions such as a popsicle and re-direction, which is standard of care at participating centers.

Regardless of investigational arm, if a child scores positive for emergence delirium using the attached PAED scale, the anesthesiologist may choose to treat this with 0.25-1ug/kg Dexmedetomidine, maximum 50ug. Dosing will occur at the provider's discretion and will be documented.

Use of other NSAIDs: Administering post-op Ketorolac in PACU is prohibited for both groups.

Recently, CHOP ENT departmental clinical practice has been changed regarding the use of pre-operative Celebrex. Surgeons at CHOP have begun to prescribe Celecoxib to be taken on the morning of (before) the scheduled surgery. While the intent is to reduce postoperative pain, there is a paucity of evidence that this preoperative dose does so. In addition, this practice is followed by most but not all members of CHOP Otolaryngology Department and is not done widely outside of this participating center. Furthermore, many participating centers' patients are unable to take Celecoxib because of age or insurance reasons. If patients are interested to in the study, they will be instructed to not take Celecoxib the morning of surgery by their surgeon. There is no evidence to believe that this will have any impact on their intra-operative or immediate post-operative course. The participating center Otolaryngologists have all agreed to instruct their patients to not take Celecoxib the morning of surgery for the purposes of the study. As noted in the PACU and home sections, all other medications routinely used for pain will not be changed by the study.

At home, patients will be prescribed one of three well-established regimens that is determined by their surgeon: liquid Oxycodone and Acetaminophen (not currently prescribed by surgeons who have opted to participate), Acetaminophen and Ibuprofen with a rescue prescription for Oxycodone and Acetaminophen and Celecoxib with a rescue prescription for Oxycodone. Because of the range of doses by weight and age, each patient is provided with a customized discharge medication list (prepared by their surgeon) prior to leaving the hospital.

Morphine, Fentanyl, Oxycodone, Acetaminophen, Dexmedetomidine and Ketorolac are currently used frequently in participating center clinical pediatric anesthesia practice. The dose, route, and indication are standard of care for pediatric patients at participating center, although Ketorolac is not the standard of care for tonsillectomy at participating center. Dexmedetomidine and Ketorolac are FDA approved medications for adults only but are on the participating center formulary and are frequently used. Ketorolac has a Black Box warning associated with the following systemic risks: Gastrointestinal (peptic ulcers, gastrointestinal bleeding, and/or perforation of the stomach or intestines), Cardiovascular (serious thrombotic events, myocardial infarction and stroke), Renal (avoid with advanced renal impairment and in patients at risk for renal failure due to hypovolemia), Risk of Bleeding (contraindicated in patients with suspected or confirmed cerebrovascular bleeding due to inhibition of platelet function, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding). Any patient identified with factors that place them at increased risk of bleeding are excluded from study participation. Ketorolac, and other non-specific NSAIDs have been associated with a small increased risk of bleeding after all surgical procedures. The sentinel Strom publication evaluated the risk of operative site bleeding among patients who had received 10, 272 parenteral Ketorolac doses compared to matched patients who received opioids and found that there was a slight non-significant elevation in adult patients (OR 1.02; 95% CI 0.95-1.10).[22] The POINT trial compared risks of serious adverse events, including increased surgical site bleeding, gastrointestinal bleeding, acute renal failure and allergic reactions, between 11,245 patients who were randomized to receive Ketorolac, Ketoprofen and Diclofenac.[23] At the time, safety data were inconclusive with regard to Ketorolac compared to the other two non-steroidal anti-inflammatory agents. There were no significant differences for the key outcomes between all three groups (Forrest 2002; Br J Anaes). Historically, Ketorolac, as well as other NSAIDs, were associated with an increased risk of bleeding after tonsillectomy. [24] Patients will receive information in the consent that some studies have linked Ketorolac administration to a higher risk of bleeding, especially in adults and when multiple or high doses (>0.5mg/kg) are administered. The modern standard of care involves use of cautery, and the procedural risk of bleeding peaks 5-10 days after surgery when the eschar begins to dislodge in the oropharynx; Ketorolac's terminal duration of action is 30 hours.[25] A sentinel 2014 meta-analysis concluded that there was no increased risk of post-tonsillectomy hemorrhage in children who received Ketorolac for tonsillectomy, but the authors reported that the risk appeared to have a five-fold elevation among adults.[25] This meta-analysis specifically notes that the adult data are under-powered relative to the pediatric data to detect a difference in bleeding risk, but it must be emphasized that the association between Ketorolac use and bleeding was significant in adults.[25] In a newer cohort study of adults undergoing tonsillectomy who received either a five-day course of oral Ketorolac versus a traditional opioid-containing regimen, there was no significant difference between postoperative hemorrhage between groups and there was no difference in severity of bleeding events.[26] However, this study was not adequately powered to detect a significant difference. For adults, it is still unclear if the risk of bleeding after tonsillectomy is higher with Ketorolac given the small number of patients who undergo tonsillectomy as adults and the higher risk of bleeding.[25,26]Of note, Dexmedetomidine and Ketorolac are two medications are frequently used in combination (after excluding patients less than 44 weeks post- conceptual age and at risk for renal insufficency or increased bleeding risk) without increase in risk, specifically for urologic, orthopedic and otolaryngology procedures *(*personal communication, **Dr. Francis Kraemer**, Chief, Acute and Chronic Pain Management, Department of Anesthesiology, 11 Oct 2019). However, this is not the current standard of care at participating center for tonsillectomy.

IND exemption form applications are attached.

1) Both Dexmedetomidine and Ketorolac are lawfully marketed in the United States.

2) Their use in this study is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use the information that is collected to support any other significant change in the labeling of the drug or advertising of the drug,

3) Their use does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with their use.

Dexmedetomidine and ketorolac will be supplied by participating center hospital pharmacy like all other anesthetic medications for the surgery. The drugs are included in participating center standard OR anesthesia cart. Investigational Pharmacy will not be involved in this study.

7.1.1 Dosing

OFG investigational group:

Dexmedetomidine is 1μg/kg with maximum 50 μg intravenously
Ketorolac is up to 0.5mg/kg with maximum 15 mg intravenously. Although 30mg is recognized at the maximum dose at participating centers, there is evidence to support dose capping at 15mg given decreasing analgesic effect and the possibility of increased risk with higher doses.[21]

All other medications are dosed in compliance with participating center standards as noted in Section 7.1.

7.1.2 Treatment Compliance and Adherence

The anesthesiologist will be notified of the randomization assignment from a study member. As noted in exclusion criteria, any patient at high risk of hemorrhage secondary to a bleeding disorder diagnosis would be excluded from study participation. If a surgeon were to feel that the surgical bed was not hemostatic, they would notify the attending anesthesiologist prior to disclosure of the treatment arm and any patients randomized to the intervention arm would be crossed-over to the TCG and analyzed separately. This is not anticipated based upon data provided by our colleagues at Seattle Children's Hospital for 965 consecutively enrolled patients. Patients will be expected to respond to POD 1, 5 and 30 text queries. Study staff will follow-up within two days if these queries are not completed. Any loss to follow-up will be documented and released with the final data analysis.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study. AE/SAEs will be evaluated by a blinded study investigator. Our stopping criteria are as follows: if a maximum expected 10% risk of bleeding is exceeded in a given month, the trial will be halted, the IRB will be notified and the DSMB will conduct an audit to assess if the risk is higher in one group. The interim analysis will occur after 50 patients, 15% of the target, have been enrolled. The DSMB board will meet at this point. In addition, the DSMB will have planned semi-annual meetings to review data and a meeting may be called by any investigator or participating center's clinician to review specific concerns. The DSMB will also receive monthly reports detailing bleeding rates in the two groups. The IRB will be immediately notified, and the study will be halted while the DSMB examines the data if significant, unexpected deviations are detected. If the DSMB determines that the rate increase was similar between groups and had no plausible correlation with Ketorolac or other study medications (i.e. new surgical technique or operator with a higher rate of surgical complications), the study would be permitted to proceed.

The following are anticipated SAEs for pediatric tonsillectomy at our institution.

The following are the known SAEs related to surgery that are anticipated based on current clinical experience, and the approximate rates that are expected. These SAEs will be recorded and their rates monitored carefully, but are reported differently to the IRB from the unanticipated SAEs.

1. Postoperative hemorrhage (expected rate up to 10%)

Hemorrhage is not rare after tonsillectomy, and is anticipated in both treatment groups. Rates are typically 2-5%, but rates up to 10% have been observed in some months at participating center. Hemorrhage is always considered a life-threatening SAE. We further anticipate that rates of the two groups will be similar.
Hemorrhage events, including hospitalization and surgical management, will be recorded, and their rates and outcomes monitored by the PI throughout the study.

2. Postoperative readmission (expected rate up to 10%).

From internal quality monitoring data over the last 2 years, rates of readmission of up to 10% have been observed. Historically these result from hemorrhage (described separately above), pain-related complications (uncontrolled pain, dehydration), and side effects from narcotics or anesthesia (e.g., nausea, vomiting).

3. Prolonged initial admission (expected rate up to 30% of those kept overnight).

Children who are admitted overnight after surgery often stay hospitalized a second night or longer. The most common reason is inadequate oral intake, which is most common in the younger children. Other reasons include inadequate pain control, the need for more time to wean off supplemental oxygen, or the need for an additional night of respiratory monitoring due to episodes of oxygen desaturation recorded the first night.

Some admissions, however, are pre-planned and the standard of care for certain populations (i.e. age, disease severity, co-morbidities, or other considerations). These planned admissions are not considered as serious safety events.

8.2 Adverse Event Reporting

If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs in access of expected SAEs and expected ranges) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

Specifically, with regard to bleeding risk (although this plan also includes re-admission and prolonged initial admission), if bleeding in either cohort exceeds expected rates (10% during one month), the IRB will be notified as noted below and the DSMB will conduct a data audit. All FDA regulations and IRB policies will be followed. Study enrollment will be halted until input has been obtained from all Data and Safety monitoring team members listed below and the IRB office.

As noted in Section 8.1, when the 50th patient is enrolled and/or if the bleeding rate exceeds 10% in one month, treatment groups will be blinded and bleeding events will be presented to the DSMB. If the DSMB agrees that the rate of the bleeding is not different from baseline established rates, the study will be permitted to proceed. The DSMB will have planned semi-annual meetings to review data and a meeting may be called by any investigator or CHOP clinician to review specific concerns. The study's primary study coordinator will tally adverse events and will provide these to the DSMB each month.

To provide an additional level of oversight, two well-qualified pediatric physician researchers will

participate in the evaluation of a severe adverse event, including bleeding in excess of established rates. These individuals are:

- **Dr. Todd Kilbaugh,** an experienced translational researcher and intensivist at CHOP
- **Dr. Sydney Brown,** a PhD-level Epidemiologist with significant experience in ethical study conduct and a practicing Anesthesiologist at CHOP
- In the event of discordance, **Dr. Ian Yuan,** a clinical researcher who specializes in assessment of anesthetic depth in neonates, will step in to perform a third assessment.

The Investigator will promptly notify the local IRB of all unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below.

Type of Unanticipated Problem	**Initial Notification (Phone, Email, Fax)**	**Written Report**
Death or Life Threatening SAEs (not listed in Section 8.1)*	24 hours	Within 2 calendar days
All other SAEs (not listed in Section 8.1)*	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

*For the ***Anticipated SAEs*** listed in Section 8.1 above, the Investigator will report these events differently than other SAEs. If rates of ***Anticipated SAEs*** fall within the expected ranges listed in Section 8.1, they will be reported similarly to AEs, as a summary at the time of Continuing Review. However, if their rates exceed the expected ranges, they will be reported promptly to the IRB as per the above table (i.e., 24 hours for life threatening SAEs, 7 days for all other SAEs). Death will always be reported within 24 hours regardless of the circumstances.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

The randomization schedule will be generated by a statistician at DCC and randomized by using the REDCap randomization feature. The subject is required to be registered in REDCap prior to randomization. To avoid protocol deviation, only eligible subjects are able to be randomized in REDCap by a designated unblind study staff.

9.1.2 Blinding

The study has blinded and unblinded staff.

The unblinded members are the treating anesthesiologist for the case, staff who randomize, and collect and enter medications into REDCap. The otolaryngologist will remain blinded. All staff and parents could

be un- blinded once the 30 day chart review and AE/SAE evaluations are completed. Group randomization assignment in REDCap will be only visible to limited unblinded staff including the study manager and data entry staff.

Blinded members include the subject and their family members, the surgeon, staff who will perform post-op assessment, and at least one physician investigator who will perform any AE/SAE assessments. Statistician and DSMB should also be kept as blinded.

9.1.3 Unblinding

Subject intra-op medication will be unblinded and documented in eMR. If the "blinded" assessor is unblinded at the time of assessment, then unblinded date and reason will be documented in REDCap. Another blinded staff may be assigned for the remaining assessments.

9.2 Data Collection and Management

Minimal identifiable information might be printed and recorded on paper for study eligibility clarification, study data collection, and data validation. Paper records which contain direct PHI will be stored in either locked file cabinets or in a secured locked research staff or investigator's office with access only to authorized personnel. Study data will be stored on a participating center password protected research drive with access limited to research personnel. REDCap will be utilized to capture study data.

When the study is completed, all study paper records may be scanned to store along with other electronic study records for retention. All study materials including PHI will be retained for 6 years post-study completion per institutional data retention policy. Paper consent forms will be scanned and uploaded into study REDCap for retention.

Master List sharing will be limited among the research team. Limited dataset with dates will be shared with the statistician for data analysis.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with institutional policies and HIPAA on subject privacy. No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at DCC) before sharing a limited dataset. Safeguards to maintain subject confidentiality are described under Data Collection and Management.

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

This is a greater than minimal risk study, and there are stringent exclusion criteria given the risks associated with the study medications (specifically bradycardia and higher bleeding risk) in small sub-sets of the surgical population. The data monitoring plan is outlined in Section 8.2, and we have consulted with two external experts in pain research and ethical research conduct. During the study period, the DSMB and PI will monitor study progress, ensure subject safety, and the accuracy and security of the data at participating certers, and will report any adverse events in accordance with the FDA regulations and IRB policies.

9.4.2 Risk Assessment

Dexmedetomidine and Ketorolac are currently used frequently in participating center clinical pediatric anesthesia practice (see Appendix II and III), although Ketorolac is not the standard of care for tonsillectomy at participating center. There is no reason to suspect an increase in risk from their use in this

study after children with risk of complications have been excluded from participation, although there is evidence that adults are at higher risk of bleeding with Ketorolac administration.[27,28] Many otolaryngologists, along with the entire anesthesia department, have agreed to have their patients randomized. There is the possibility that OFG subjects' pain will not be adequately controlled without opioids. If the pain is not controlled in the OFG group they will receive opioids in the same manner as the TCG group where severe pain is managed with additional opioids.

Risks of Ketorolac: While Ketorolac is routinely given to children at participating centersfor certain procedures, it is not FDA approved for use in children. Its use is increasing for tonsillectomy, but it is not the standard of care at participating center and is only used by a sub-set of Otolaryngologists (nine have agreed to have their patients randomized to receive Ketorolac). Some surgeons avoid Ketorolac entirely. As noted in more detail below, historic data found that there was an increased risk of bleeding after tonsillectomy with Ketorolac administration and may be related to excessively high doses that were administered. The FDA label also warns that Ketorolac can cause peptic ulcers, stomach bleeding and holes in the stomach, which is why it is never used more than five days in a row. All non-steroidal anti-inflammatory drugs (NSAIDs), like Ketorolac and Ibuprofen, have a similar risk profile, although these risks may be higher with the IV formulation. There is a black box risk associated with increased bleeding. All children with bleeding disorders or certain kidney problems are excluded from participation.

Ketorolac, and other non-specific NSAIDs have been associated with a small increased risk of bleeding after all surgical procedures. The sentinel Strom publication evaluated the risk of operative site bleeding among patients who had received 10, 272 parenteral Ketorolac doses compared to matched patients who received opioids and found that there was a slight non-significant elevation in adult patients (OR 1.02; 95% CI 0.95-1.10).[22] The POINT trial compared risks of serious adverse events, including increased surgical site bleeding, gastrointestinal bleeding, acute renal failure and allergic reactions, between 11,245 patients who were randomized to receive Ketorolac, Ketoprofen and Diclofenac.[23] At the time, safety data were inconclusive with regard to Ketorolac compared to the other two non-steroidal anti-inflammatory agents. There were no significant differences for the key outcomes between all three groups.[23] Historically, Ketorolac, as well as other NSAIDs, were associated with an increased risk of bleeding after tonsillectomy.[24] With current surgical technique, the procedural risk of bleeding peaks 5-10 days after surgery when the eschar begins to dislodge in the oropharynx.[25] A sentinel 2014 meta-analysis concluded that there was no increased risk of post-tonsillectomy hemorrhage in children who received Ketorolac for tonsillectomy, but the authors reported that the risk appeared to have a five-fold elevation among adults.[25] This meta-analysis specifically notes that the adult data are under-powered relative to the pediatric data to detect a difference in bleeding risk, but it must be emphasized that the association between Ketorolac use and bleeding was statistically significant in adults.[25] In a newer cohort study of adults undergoing tonsillectomy who received either a five-day course of oral Ketorolac versus a traditional opioid-containing regimen, there was no significant difference between postoperative hemorrhage between groups and there was no difference in severity of bleeding events.[26] It is currently unclear if adults are at higher risk of hemorrhage after tonsillectomy with Ketorolac administration.[25,26]

Risks of Dexmedetomidine: Dexmedetomidine is part of a group of medications called Alpha-2 agonists that provides pain control and causes sedation but has negligible impact on respiratory drive. The primary risk is a decrease in heart rate, which is why children with unrepaired congenital cardiac disease or syndromes with predisposition to bradycardia are excluded from participation. If severe bradycardia developed, it would be medically treated with either Atropine or Glycopyrrolate.
Risk of the combination of Ketorolac and Dexmedetomidine: There is no increased risk of giving these two medications together.

9.4.3 Potential Benefits of Trial Participation

Subjects who are randomized to the OF Group will likely avoid a potentially high-risk opioid exposure. In

addition, it is likely that the incidence of nausea and vomiting will be significantly reduced. The Opioid-Free technique could reduce hundreds of thousands of annual pediatric opioid exposures, and subsequent risk of misuse among pediatric patients.

9.4.4 Risk-Benefit Assessment

There are potential benefits to the greater population of children in that we will have knowledge with regard to outcomes and satisfaction for the opioid-free technique for tonsillectomy.

9.5 Recruitment Strategy

The PI will provide an in-service to all recruiting locations at participating centers. Potential subjects will be identified from the scheduled surgical list. The study introduction will be initiated by any study investigator.

The risks and benefits will be discussed at the consent conference. The study research flyer could be given to each potential subject/family either at the pre-op clinic visit (in-person) or via email/text with link to the informed consent form .The family could view consent form via the link or scan QR code on the flyer. After study information has been provided, a member of the study staff screens interested patients and reviews inclusion and exclusion criteria as described in the Screening Visit section.

9.6 Informed Consent/Assent and HIPAA Authorization

A combined consent-authorization document will be used. Only one signature from parent or legal guardian will be required for this study.

For the subjects who were unable to perform the Informed Consent process at the clinic visit prior to the day of surgery or require additional time to review the study documents and consent form, the following will occur. A Study Team member will telephone, email, or send text via REDCap, which includes a link to referral form, to the potential subject any time after ENT pre-clinic visit but before the scheduled surgery day depending on the family's availability, explain the study to them, and perform screening assessments as described above. The text message or email which contains the link to download the study consent will only be sent to permissible subjects/families after the study has been briefly been introduced and subjects/families have expressed interest in learning more.

The actual Informed Consent/Assent process will occur as follows. A study physician will be immediately available by telephone to answer any questions about the study procedures or risks. The formal consent discussion (including discussion of risks like bleeding) will not occur on the day of surgery. The consent discussion will occur in advance (and will be documented in the study REDCap), but it is acceptable for the signed form to be returned on the day of surgery or to be signed on the day of surgery.

The consent interview could also be conducted by telephone when the parent can read the consent form during the discussion (and when the child is available for assent, if applicable). The consent form will be signed either before or on the day of surgery. The parent will have the opportunity to ask questions and receive answers prior to signing the form. A study physician will either be immediately available during the call to answer any questions about the study procedures or risks, or the parent will be given a description of how and when they will receive answers to their questions (usually by a telephone call later from the physician) prior to the date of surgery. Family will be informed during the consent process that they might not be able to participate even if consented due to unexpected circumstances such as rescheduling, limited researcher availability, and eligibility. Consent will be conducted in a private area.

Regardless of method of obtaining consent, subjects will be instructed to not sign the document until all questions they have for a physician are answered. Subjects are counseled that they may freely choose not to participate in the study, but if so, they will not receive an opioid-free anesthetic. They will be informed that this will not otherwise affect their other medical care or treatment. In particular, it will be emphasized that

their pain control would follow standard of care outside the study, and that they will still obtain the recommended surgery in the usual fashion. Families will also be counseled that they will be responsible for costs of care not covered by their insurance and that participating center does have additional resources if they are uninsured or underinsured. Families are given as much time as they need to make their decision and ask questions of the staff and physician, who will ensure that subjects comprehend the nature of the study, the study procedures and the risks and benefits of participation before providing consent.

9.7 Payment to Subjects/Families

There will be no payment to subjects/families.

10 PUBLICATION

After collection, review, and analysis of data, the results of this study will be submitted for publication in a peer-reviewed scientific journal.

The study is funded by participating center local grant.

APPENDIX I:

Baseline Questionnaire

1. Have any other children living in your household had a tonsillectomy and/or adenoidectomy? (Yes)/(No)
2. Has anyone in (Child's Name) taken opioids in the past 30 days? (Yes)/(No)
3. Does (Child's Name) have pain today? (Yes)/(No)
4. Has your child said they have pain anywhere in their body in the last 30 days?
5. If yes, how would you rate it on a scale of 1-10 (1 meaning very mild pain, 10 meaning the worst pain of their life)
6. Has your child been given opioid medications (i.e. oxycodone, morphine, etc.) for pain control within 30 days?

Questionnaire for POD1 and POD5, POD30

*The same questionnaire will be asked (either by electronic questionnaire or via phone, if indicated as the family's preference) on POD5 and POD30.

1. Are you satisfied with your child's recovery?
   - 1-7 Likert scale

Strongly agree	Agree	More or less agree	Undecided	More or less disagree	Disagree	Strongly disagree
(1)	(2)	(3)	(4)	(5)	(6)	(7)

2. Are you satisfied with your child's pain control at home?
   - 1-7 Likert scale

Strongly agree	Agree	More or less agree	Undecided	More or less disagree	Disagree	Strongly disagree
(1)	(2)	(3)	(4)	(5)	(6)	(7)

3. Did your child experience severe nausea or vomit after leaving the recovery room (POD1 questionnaire only)

4. How would you rate your child's pain today (have your child provide assessment if age appropriate) on the provided pain scales (Modified Bieri <10 years, NRS ≥10years)

   - For POD5 survey only; please fill in the average pain score for POD2, POD3, POD4 and POD5 (today)

5. Have you given your child any Acetaminophen (Tylenol)?
   - If yes: Fill in number of total doses [by day]
6. Have you given your child any Celecoxib (Celebrex) or Ibuprofen (Motrin)?
   - If yes: Fill in number of total doses [by day]
7. Did you receive a prescription for oxycodone?
   - If yes, did you fill this prescription?
   - If you filled this prescription, how many tablets has your child used?
8. Will be completed by phone for POD1: Has your child had any bright red blood in their mouth? (yes/no)
   - If yes, please insert date/time of event
   - Were you/your child evaluated in an outside ER or hospital. If so, was admission and/or reoperation required?
9. Will be completed by phone for POD1: Has your child not met any of the hydration guidelines that were provided prior to discharge? (yes/no)

Phone Script for questions 8 and 9:

Provider: My name is XXX and I am a research (physician or nurse) with the Opioid-free tonsillectomy study. I am calling to see how your child has been doing since they went home yesterday. [Will ask questions 8 and 9]. If both answers are no, the provider will state, "if you would like, I can complete the rest of survey questions [1-7] with you on the phone right now". At the end, the provider will state, "Thank you for your time"

1. Will be completed by phone for POD1: Has your child had any bright red blood in their mouth? (yes/no)
2. Will be completed by phone for POD1: Has your child been drinking and making urine? (yes/no)

If subjects respond with "yes" to bleeding and/or "no" to drinking and making urine they will be called by a study MD (if RN is making the POD1 call) and be directed to the participating center's Emergency Department for assessment (or the local hospital if closer with coordination with the surgeon's office) and the patient's participating center surgeon will be notified for follow-up. If dehydration is detected, the patient will be directed to have their Creatinine checked. The date of a bleeding (including time of event if it occurs on POD1) or dehydration event will be captured in RedCap by the research staff.

Please note that you will receive a call from the study team and/or the Otolaryngology clinic if you answer Yes to either Question 8 or 9 on POD5 or POD30*

3. Day 30 only: Did you see a doctor or nurse outside of participating center for:
    - Bleeding, poor pain control, severe nausea, constipation, dehydration and/or inability to take in adequate nutrition

      A study doctor will contact you to learn more about your child's experience.

Appendix II: Case for IND Exemption, Ketorolac for Tonsillectomy

Whether an IND is needed to conduct a clinical investigation of a marketed drug primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation. A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:

- The drug product is lawfully marketed in the United States.

Ketorolac is lawfully marketed in the US.

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of Ketorolac.

The study is not intended to support a new indication or change in labeling of Ketorolac.

- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for Ketorolac.

The study does not intend to support a change in advertising of Ketorolac.

- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

The route of administration matches the product label (intravenous).

For the population to be studied, children aged 2-18 undergoing tonsillectomy, the investigators do not consider this population to be at added risk for the indication, pain control, for which this medication has been approved by the participating center formulary (30mg dose equivalent to 12mg morphine). The Ketorolac dose planned for the study is equivalent to the approved dose (0.5mg/kg, maximum 30mg; of note, the study maximum is set more conservatively at 15mg). Many patients undergoing tonsillectomy have a sleep- disordered breathing diagnosis that is worsened by administration of opioid pain medications, for which Ketorolac provides equivalent analgesia (i.e. a 10kg child would routinely receive 0.1mg/kg, or 1mg morphine intra-operatively, and the participating center formulary analgesic equivalent dose for Ketorolac would be 2.5mg, well below the acceptable 0.5mg/kg dose of 5mg). A prospective randomized controlled trial found that children with sleep-disordered breathing who were exposed to opioids perioperatively had an average increase of 11.17 (+/-15.02) desaturation events per hour.[6] Per the participating center formulary, children with renal dysfunction or a bleeding disorder would be ineligible to receive Ketorolac.

Historically, there was concern that non-steroidal anti-inflammatory drugs (NSAIDs) were related to an increased bleeding risk among children undergoing tonsillectomy. Several contradictory studies were underpowered to detect bleeding risk; the concern for bleeding risk exists 7-10 days after surgery.[29,30] Ketorolac's half-life is 5-6 hours and any change in platelet function returns to baseline 24-30 hours after a single dose, well before the period associated with higher bleeding risk.[31,32] A large meta-analysis demonstrated that there is no increased risk of post-tonsillectomy bleeding in children under 18 years, however, the same study identified a 5-fold increased bleeding risk among adults and this was statistically significant.[25,26] Of note, oral NSAIDS, along with acetaminophen, are now the standard of care for post- operative analgesia for tonsillectomy, and a large internal retrospective review noted no increased risk of post-tonsillectomy bleeding with NSAID administration post-operatively.[33,34]

Although there are little published data, Ketorolac is routinely used at similar sites such as DuPont Hospital for Children, Emory, Albany Children's and Seattle Children's without evidence of increased bleeding risk among children undergoing tonsillectomy. Seattle Children's has transitioned to the same opioid-free protocol listed in the study application. Data output obtained via a quality improvement initiative at Seattle Children's are notable for no increased bleeding risk (return to OR rate is 0.8 among 612 patients undergoing the opioid-free protocol with Ketorolac and 1.17% among 1,724 children receiving a standard opioid-containing protocol), no significance in maximum post-operative pain score and a decrease in post-operative nausea and vomiting (see Figure 1; personal communication, Dr.

Daniel Low, June 28 2019). Seattle Children's continues to provide monthly data updates to the investigators and has already treated 965 pediatric patients (up to age 19), more than the number proposed in this Year 1 protocol. Emory and Albany have published trial protocols on clinicaltrials.gov with the intent of demonstrating decrease in post-operative opioid requirements by using Ketorolac for tonsillectomy in children (NCT03453541 and NCT03467750).

Therefore, the investigative team believes that the use of Ketorolac in the study is IND exempt, and that there is no increased risk or decreased acceptability of the risk, of administering 0.5mg/kg of Ketorolac to children age 2-18 undergoing tonsillectomy.

Table 1**: Literature review of Ketorolac dose algorithms and adverse events in pediatric patients undergoing tonsillectomy.**

Author	**N**	**Age**	**Dose**	**Adverse Events**
Chan 2014[25]	Meta-analysis of 10 studies reporting ketorolac administration and bleeding risk	Under 18	Variable	Relative risk of any bleeding under age 18: 1.39; 95% CI: 0.84–2.30; p=0.20; conclusion that there is no increased risk of bleeding under age 18 with ketorolac administration (either intra- or post-operatively) for tonsillectomy
Low 2019 (QI data, see Figure 1)	612 children	Age 2-19	0.5mg/kg, maximum 30mg	Return to OR for bleeding among 0.79% of children receiving Ketorolac; 1.17% among children receiving morphine/acetaminophen

Figure 1. Summary of quality improvement data, Seattle Children's (through 6/28/2019)

• The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

The study will be conducted after IRB approval, with an IRB-approved consent.

• The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

The study is not intended to promote or commercialize the drug product.

Appendix III: Case for IND Exemption, Dexmedetomidine for Tonsillectomy

Whether an IND is needed to conduct a clinical investigation of a marketed drug primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation. A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:

• The drug product is lawfully marketed in the United States.

Dexmedetomidine is lawfully marketed in the US.

• The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of Dexmedetomidine.

The study is not intended to support a new indication or change in labeling of Dexmedetomidine.

• In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for Dexmedetomidine.

The study does not intend to support a change in advertising of Dexmedetomidine.

• The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

The route of administration matches the product label (intravenous).

For the population to be studied, children aged 2-18 undergoing tonsillectomy, the investigators do not consider this population to be at added risk for the indication, procedural sedation and anesthesia, for which this medication has been approved by the participating center formulary. The Dexmedetomidine dose planned for the study will not exceed the approved dose. Dexmedetomidine has been approved at participating center for infants and children up to doses of 2ug/kg for procedures; our study proposes 1ug/kg (maximum 50ug). Many patients undergoing tonsillectomy have a sleep-disordered breathing diagnosis that is worsened by administration of opioid pain medications. A prospective randomized controlled trial found that children with sleep-disordered breathing who were exposed to opioids perioperatively had an average increase of 11.17 (+/-15.02) desaturation events per hour.[6] A randomized controlled trial demonstrated that 1ug/kg of Dexmedetomidine is equivalent to 0.1mg/kg morphine for post-operative analgesia for tonsillectomy without the respiratory depression and nausea risk associated with opioids.[28] There are extensive data with regard to the safety of Dexmedetomidine use in the pediatric population for sedation; additional benefits include protection against end-organ ischemia.[35,36] Dexmedetomidine has been studied in children undergoing tonsillectomy and was found to significantly reduce the risk of emergence delirium without causing an increase in extubation time or hemodynamic changes. [27,37] Therefore, the investigative team believes that the use of dexmedetomidine in the current study is IND exempt, and that there is no increased risk or decreased acceptability of the risk, of administering 1ug/kg of Dexmedetomidine to children age 2-18 undergoing tonsillectomy.

Table 1: Literature review of Dexmedetomidine dose algorithms and adverse events in pediatric patients.

Author	N	Age	Dose	Adverse Events
Olutoye[28]	109	Mean age 6.4 years (3-12 years)	Drug was administered by infusion over ten minutes at 0.5ug/kg and 1ug/kg	Assessed; None related to drug use
Gupta[35]	94 (52 receiving drug)	Mean age 10.5 months (infant-18 years; 5.0 months in control group)	Drug administered as infusion ≥96hrs at 0.3-1.0ug/kg/hr.	One patient experienced junctional heart rate at 130 beats/min requiring pacing (critically ill children with cardiac disease; unclear if drug related). Group receiving drug had decreased inotrope, opioids and benzodiazepine requirements
Patel[27]	122 (61 receiving drug)	Mean age 4.0 years (2-10 years)	Drug was administered as 2ug/kg bolus over 10 minutes, followed by 0.7ug/kg/hr infusion	Assessed; None related to drug use. Decreased post-operative opioid doses, desaturation events and emergence delirium.
Tsiotou[37]	60 (31 receiving drug)	Mean age 6.2 years (3-14 years)	Drug was administered as a 1ug/kg bolus over 10 minutes	Assessed; None related to drug use. Three-fold decrease in emergence delirium risk

• The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

The study will be conducted after IRB approval, with an IRB-approved consent.

• The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

The study is not intended to promote or commercialize the drug product.

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