Massachusetts Eye and Ear Infirmary

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Form I - Protocol Application

IRBNet ID:	242942-1
HSC Protocol #:	
Principal Investigator Name:	Christopher Hartnick, MD
Date:	6/1/2016
Project Title:	Postoperative Ibuprofen and the Risk of Bleeding After Tonsillectomy with or without Adenoidectomy
Funding Source:	Intradepartmental Funds

***To mark a 'check' box, click on the item you would like to select and type an 'x'. For all other questions, click on the area below the question to type your response.**

The Core Data Form needs to be completed online and submitted along this application.

This form must be filled out completely. Do not leave any sections blank. If a field does not apply to your research state so using the abbreviation "NA". For any items described in the sponsor's protocol or other documents submitted with the application, you may reference the title and page numbers of these documents. If you reference page numbers, attach those pages to this protocol application package. Limit attached pages to those referenced in this protocol.

1a. Collaborating Institution(s): Please list any institution involved in the study and the status of IRB approval.

Response: Madigan Army Base, Naval Medical Center of San Diego, Brooke Army Medical Center, Naval Medical Center, Portsmouth, VA.

1b. Where will the study take place? Please list all locations outside of 243 Charles street where human subjects research related to this study is expected to occur.

Response: Madigan Army Base; Tacoma, WA; Naval Medical Center of San Diego, Department of Otolaryngology; San Diego, CA; Brooke Army Medical Center, Department of Otolaryngology; San Antonio, TX; Naval Medical Center, Department of Otolaryngology; Portsmouth, VA.

2. In layperson's language please state the purpose of this study in 3-5 sentences.

Response: Tonsillectomy (the surgical removal of the tonsils) is a commonly performed surgery in children. One risk of tonsillectomy is postoperative bleeding, and this can be more dangerous in children because their blood volume is lower than adults. Ibuprofen, a nonsteroidal anti-inflammatory medication (NSAID), is an effective pain medication. Recent guidelines, published by the American Academy of Otolaryngology, advocated use of ibuprofen after tonsillectomy. However, NSAIDs are associated with altered platelet function and a theoretical increased risk of bleeding after surgery. We would like to explore the effect that ibuprofen has on postoperative bleeding, as well as validate previous studies demonstrating it is an effective pain medication after tonsillectomy.

SPECIFIC AIM

3. Please state the specific aims of the research being proposed and the hypothesis which you will be testing.

Response: Specific Aim 1: To compare the rates of post-tonsillectomy bleeding between pediatric patients who receive postoperative ibuprofen to those who receive acetaminophen in a prospective, randomized, blinded and controlled trial.

The primary objective of this study is to determine if postoperative ibuprofen at 10mg/kg dosing four times daily postoperatively for 9 days is associated with an increased rate of post-tonsillectomy bleeding requiring operative intervention for hemostasis in children when compared with acetaminophen. To achieve this, rates of post-tonsillectomy bleeding, both primary, defined as occurring < 24 hours after surgery, and secondary, defined as occurring > 24 hours after tonsillectomy, will be recorded. Additionally, distinction will be made between bleeds requiring emergency room evaluation, admission for observation, and operative control of hemorrhage.

Specific Aim 2: To compare the rates of post-tonsillectomy hemorrhage when studying different groups of patients based upon their age, indication for tonsillectomy, or operating surgeon.

The second objective of this study is to determine if bleeding rates differ according to surgical indication, age of the patient, or operating surgeon, using a multi-variate logistic regression model. This is important since indication for tonsillectomy varies in children. Younger children tend to undergo tonsillectomy for obstructive sleep symptoms whereas older children tend to undergo tonsillectomy for infectious tonsillitis.

Specific Aim 3: To evaluate effectiveness of ibuprofen as a post-tonsillectomy analgesic in comparison to Acetaminophen, which is currently the standard of care at our institution.

The third objective of this study is to evaluate the efficacy of ibuprofen at 10mg/kg dosing (max dose 600mg) at Q6 hour dosing as an analgesic in the postoperative period in comparison to Acetaminophen, 15mg/kg (max dose 650mg), which is currently the standard of care at our institution. Previous studies have determined that ibuprofen at 5mg/kg dosing is an effective

post-tonsillectomy analgesic, however 10mg/kg dosing, the maximum ibuprofen dose, has not been previously evaluated in the literature. We feel it is important to evaluate both the analgesic effect and rate of post-tonsillectomy bleeding associated with this maximum dosing if ibuprofen is to be widely used in the postoperative period after tonsillectomy.

BACKGROUND

4. Summarize the background, nature, rationale (include any previous or ongoing related HSC protocol #'s) and the significance of the proposed study.

Response: Tonsillectomy with and without adenoidectomy is one of the most commonly performed surgical procedures in the pediatric population. The incidence of adenotonsillectomy has increased over the past four decades (1). This is mainly due to increased awareness of the potential adverse consequences that pediatric sleep disordered breathing (SDB) may have on development and long-term pulmonary and cardiovascular health. SDB has surpassed recurrent tonsillitis as the most common indication for adenotonsillectomy in children (2-5). Over the past decade, according to the CDC's National Health Statistic Report on ambulatory surgery performed in the US, annual rates of tonsillectomy performed with and without adenoidectomy in children aged 15 and younger increased from 287,000 to 530,000 (6, 7). Adenotonsillectomy is the second most common procedure performed on children under the age of 15. Although generally considered a safe procedure, adenotonsillectomy has significant morbidity and potential for complications, particularly in the pediatric population. Complications include postoperative hemorrhage, dehydration, pain, anesthetic complications and airway risks, aspiration, and post-obstructive pulmonary edema (8). In young children, the risk of adenotonsillectomy is more critical due to smaller airways and respiratory reserve, as well as smaller blood volume (5).

Postoperative bleeding can be categorized as a primary event, occurring < 24 hours after surgery, or a secondary event, occurring >24 hours after tonsillectomy. Additionally, events can be further described by the interventions taken, such as emergency room visits, admission for observation, or return to the operating room to achieve hemostasis. Postoperative bleeding rates, including both primary and secondary events, range from 3.3-20%, with a mean of 4.5% (9). Thus, annually, tens of thousands of children experience exposure to potentially life-threatening postoperative hemorrhage, often requiring readmission, anesthetic exposure, and operative control of hemorrhage.

Postoperative pain contributes significantly to post-tonsillectomy morbidity. While narcotics are effective in controlling postoperative pain, they are often contraindicated, particularly in children with sleep disordered breathing, because of their potentially adverse side effects on respiration and the central nervous system (10). Nonsteroidal anti-inflammatories (NSAIDS), which block prostaglandin-induced inflammation and edema, are an attractive therapeutic option because they do not result in respiratory and central nervous system depression, and therefore may reduce the risk of postoperative respiratory depression, nausea and vomiting, excessive sedation and urinary retention. NSAIDS have been shown to be effective analgesics after tonsillectomy (11,12).

However, because their mechanism of action may also interfere with platelet aggregation and increase bleeding time, their use is balanced with concern about an increased risk of postoperative hemorrhage. Aspirin, which irreversibly inhibits cyclooxygenase, affects coagulation and bleeding for up to 10 days, has been associated with an increased bleed rate after tonsillectomy (13). However, non-aspirin NSAIDs demonstrate a reversible inhibition of COX-1 and COX-2, and therefore do not have the same severe, prolonged effects on bleeding (14). Ibuprofen, a derivative of propionic acid, is widely used for musculoskeletal pain, but the study of its use for post-tonsillectomy analgesia is limited.

In 2011, The American Academy of Otolaryngology published Clinical Practice Guidelines outlining evidence-based selection and perioperative management strategies for tonsillectomy in children. As part of a recommendation that clinicians educate caregivers about the importance of postoperative pain management, Baugh et al advocated the use of ibuprofen postoperatively, stating, "ibuprofen can be used safely for pain control after surgery" (15), citing a 2005 Cochrane Review of NSAIDs and post-tonsillectomy bleeding in support of this guideline (16). The Cochrane Review recently added additional studies to their analysis and results remained similar. The most recent Cochrane Review, published in 2010, evaluated 15 randomized trials comparing NSAIDs with other analgesics or placebo, and determined that NSAID use did not significantly alter the number of perioperative bleeding episodes, both requiring and not requiring surgical intervention; this review did not distinguish between primary and secondary bleeding events (17). Because post-tonsillectomy hemorrhage is an uncommon event, a large number of participants is required to provide an adequate number of events to give a significant result, therefore the large sample size of >1000 children in the Cochrane Review is admirable. However, sample sizes were not adequate to compare the risk of bleeding with each individual NSAID. Additionally, NSAIDs were given in both oral and parenteral forms, as well as preoperatively, intraoperatively and postoperatively, and the duration of postoperative analgesic use differed between studies. The surgical technique used was not uniform between studies as well. It is our feeling that because of these limitations, the data is not sufficient to broadly implement the Academy's recommendation that ibuprofen can be safely used for post-tonsillectomy analgesia without more carefully controlled, prospective study.

Although there are many studies in the literature evaluating NSAID use after tonsillectomy, there are few randomized-prospective trials evaluating the use of ibuprofen, and few trials are powered to adequately assess the risk of postoperative hemorrhage. Designing and executing a study to specifically evaluate ibuprofen after pediatric tonsillectomy and rates of post-operative hemorrhage requiring return to the operating room for control is important to the pediatric otolaryngology community, particularly given the American Academy of Otolaryngology's recent clinical guidelines. The results of such a definitive study would possibly affect the tens of thousands of children at risk for post-tonsillectomy hemorrhage every year. It would affect our own standards of care as well as national and international norms.

Preliminary Studies:
At the Massachusetts Eye and Ear Infirmary there is no precedent for administering ibuprofen to children after tonsillectomy with or without adenoidectomy. Despite American Academy of Otolaryngology support for the use of ibuprofen in the postoperative setting, pediatric

otolaryngologists at our institution are still hesitant to administer ibuprofen postoperatively without additional study of its use.

Within the Department of Pediatric Otolaryngology at the Massachusetts Eye and Ear Infirmary there is a precedent for successful completion of randomized, controlled trials involving adenotonsillectomy (19, 20). With principal investigators dedicated to clinical research, as well as research nurses and coordinators at our disposal, a prospective, controlled clinical trial of ibuprofen use after tonsillectomy can be implemented. Additionally, the Massachusetts Eye and Ear Infirmary calculates annual post-tonsillectomy hemorrhage rates, including percentage of patients returning to the emergency room for evaluation for possible post-operative bleeding, as well as the percentage of patients returning to the operating room for control of bleeding. Thus, there is a precedent for collecting data on postoperative bleeding events, as well as a controlled bleed rate to which prospective study hemorrhage rates can be compared.

The goal of our study is to determine if postoperative ibuprofen affects the rate of post-tonsillectomy hemorrhage using a non-inferiority trial design, which is intended to show that the effect of ibuprofen is no worse than acetaminophen, which will serve as our control. This differs from an equivalence trial, which aims to demonstrate that the experimental and control group do not differ more than a specified amount. The equivalence margin set for non-inferiority trials is often smaller than the treatment difference for which a placebo-controlled trial is powered, requiring a larger sample size. This will address two issues we have with the current literature evaluating NSAID use after tonsillectomy: inadequate sample size, and unrealistic treatment differences, including up to a 20% difference in bleed rates, required to detect a significant difference between NSAID and control groups. Because our trial will be designed to test non-inferiority, the null hypothesis will assume inferiority: the rate of hemorrhage requiring operative intervention in patients treated with postoperative ibuprofen after tonsillectomy will be increased compared to the rate in patients given acetaminophen.

References:

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16. Cardwell ME, Siviter G, Smith AF. Non-steroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. Cochrane Database Syst Rev. 2005; (2): CD003591.
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20. Collison PJ, Mettler B. Factors associated with post-tonsillectomy hemorrhage. Ear Nose Throat 2000; 79(8): 641-49.

RESEARCH PLAN

5. Provide an orderly description of the study design and research procedures including a list of assessments at each visit. If you are using a placebo, please provide justification. *If this is a clinical trial, please attach a flow chart or schema to this application package.*

Response:

Recruitment: Patients will be recruited from the practices of Drs. Hartnick, Keamy, Setlur and Cohen, as well as Dr. Diercks starting September 1, 2016 (The Massachusetts Eye and Ear

Infirmary), Drs. Boseley and Rogers (Madigan Army Base; Tacoma, WA), Brigger and Gaudreau (Naval Medical Center of San Diego, Department of Otolaryngology; San Diego, CA), Maturo (Brooke Army Medical Center, Department of Otolaryngology; San Antonio, TX), and Gallagher (Naval Medical Center, Department of Otolaryngology; Portsmouth, VA). Over the last two years, the average annual number of pediatric tonsillectomies for each collaborating investigator was approximately 200. Informed consent will be obtained for the study by the principal investigator, co-investigators, or research nurses at the time of the preoperative visit or on the day of surgery prior to arrival in the preoperative area.

Inclusion criteria: Patients ages 2-18 undergoing tonsillectomy with or without adenoidectomy by electrocautery alone for sleep disordered breathing or infectious tonsillitis. Patients with complex medical conditions and craniofacial abnormalities will be included. Only patients who are not pregnant will be included. Informed consent and child assent will be required for enrollment.

Exclusion criteria: Patients with a known personal or family history of a bleeding disorder will be excluded. Patients with a history of asthma, kidney or liver problems will also be excluded. Patients with tonsillectomy or adenoidectomy performed using a cold knife technique, microdebrider, coblation or plasma knife. Patients on NSAIDs for other medical conditions, or those who have taken NSAIDs within 1 week of surgery will be excluded. Patients with allergy to aspirin or other NSAIDs, acetaminophen, Red Dye #40 or Red Dye #33 will also be excluded. Pregnancy testing using urine beta-HCG will be performed on all children > 13 years of age, or those younger than 13 who are menstruating; this is the testing protocol used at the Children's Hospital of Boston. Patients found to be pregnant will be excluded from participation. Patients unwilling to enroll in the study will have the tonsillectomy with or without adenoidectomy performed according to current practice standards.

Randomization: Patients will be randomized upon enrollment after obtaining informed consent, and assent when indicated. Randomization will be performed centrally by the pharmacy of Massachusetts Eye and Ear Infirmary for all participating institutions. Randomization will occur via a one-to-one scheme. Randomization will be generated based on a uniform (0,1) random number generator using STATA code.

Blinding: The surgeon, nurses, and patient/parent will be blinded regarding to which arm the patient has been randomized. The pharmacy of each institution will dispense grape-flavored ibuprofen 100mg/5mL (Leader®) or grape-flavored acetaminophen 160mg/5mL (Leader®) based upon the arm to which each participant has been randomized. Ibuprofen will be dosed at 10mg/kg (max dose 600mg) and acetaminophen at 15mg/kg (max dose 650mg), dosing for each will be QID, or roughly Q6 hours when appropriate. The pharmacy will manipulate the volume of each medication using Ora Blend suspension so that for each child, weight based dosing of each medication will be equivalent in volume. Medications will be dispensed an amber colored bottle with a syringe to measure and dispense the appropriate weight based volume of each medication. Each bottle will specify the patient's name, medical record number, and the volume of medication to be dispense during each medication administration. This supply of medication will be used to dispense analgesics both while the patient is hospitalized, and upon discharge for the first 8 postoperative days.

Surgical technique: All patients will be administered 15mg/kg (max dose 650mg) of acetaminophen preoperatively prior to arrival in the preoperative area and dexamethasone 0.5mg/kg (maximum dose of 8mg) in the operating room prior to surgical commencement, which is standard practice at MEEI. The standard method of tonsillectomy among participating surgeons will be extracapsular monopolar electrocautery with standard settings of 12 watts (fulgurate) using a spatula tip. Bleeding will be controlled with suction cautery on a setting of 12-18 watts (fulgurate). Adenoidectomy will be performed at 30 watts (fulgurate). Anesthetic technique, perioperative analgesia with narcotics, and post-operative care will remain equivalent between the two study arms. Antibiotics will not be administered in the perioperative period. Postoperative anti-emetic therapy will be standardized by all collaborating physicians using standardized order sets.

Postoperative period: Postoperative antibiotics will not be administered based upon the American Academy of Otolaryngology's strong recommendation that antibiotics no longer be used for postoperative prophylaxis after adenotonsillectomy (15). For the first 8 postoperative days (9 days total, POD0-9), children will be administered weight based analgesia from medication provided by the inpatient pharmacy at MEEI four times daily while awake (roughly Q6 hour dosing). Medication will be administered from an amber colored bottle containing 36 doses of medication (QID dosing x 9 total days), which will be labeled with the child's name, medical record number, and dosing instructions. The volume of medication dispensed for each child will be manipulated with OraBlend solution such that the weight based dose of ibuprofen volume will equal the weight based dose of acetaminophen volume; both medications will be dosed QID. Surgeons, nursing staff, and patients and their families will be blinded regarding the type of medication administered (acetaminophen vs. ibuprofen). Acetaminophen will be given as 15mg/kg dosing (maximum dose 650mg) and ibuprofen will be given as 10mg/kg dosing (maximum dose 600mg). Children with breakthrough pain eligible for narcotics (based upon age, OSA status) will receive weight based doses of oxycodone 1mg/1mL elixir (0.05-0.1mg/kg) as well as be prescribed oxycodone to use for breakthrough pain as an outpatient. After 9 days, patients will be instructed to take acetaminophen 15mg/kg (max dose 650mg) every 4-6 hours as needed for breakthrough pain. They will be instructed not to use nonsteroidal anti-inflammatory drugs (NSAIDS) in the postoperative period (14 days).

Weight based ibuprofen dosing of 10mg/kg was chosen because it is the maximum dose of this medication. Previous studies evaluating ibuprofen use after tonsillectomy used ibuprofen at 5mg/kg (11,12). If ibuprofen is to be used for post-tonsillectomy analgesia, it would likely be used at the maximum dose, similar to the maximum dose of Acetaminophen (15mg/kg) already used in standard practice at our institution. Therefore, we argue that before this practice is instituted, both the analgesic effect as well as the risk of postoperative hemorrhage associated with this dosing need to be further characterized.

The decision to recommend QID dosing of analgesics for 9 days was chosen based upon previous studies which indicate that postoperative pain after extracapsular tonsillectomy using electrocautery persists above 2 on the faces pain scale-revised (range 0-6) through POD7 (19). Additionally, studies of postoperative bleeding indicate that the highest risk of incidence of

postoperative bleeding occurs on postoperative day 8 (20). Therefore, in order to assess the rate of bleeding associated with ibuprofen use, it seems reasonable to administer the drug throughout the period associated with greatest risk.

A postoperative recommendation form will be placed on each chart for review by the nurses in the recovery rom and on the floor (if inpatient status). This form will state that no additional acetaminophen be administered to the participant, and instructing that analgesia be administered from study supplied medication or supplemental narcotics if indicated for breakthrough pain at the discretion of participating surgeons. It will also have standard anti-emetic medications listed.

Pain control data will be collected using a standardized, validated questionnaires as well as additional questions regarding postoperative pain control and return to normal diet and sleep patterns (see attachment at end of proposal). These questionnaires have been used in previous studies evaluating ibuprofen and post-tonsillectomy pain (11, 12). Questionnaires for each postoperative day, as well as a 9 day supply of medication, will be dispensed at discharge. Patient's caregivers will be asked to complete the questionnaire on a daily basis for the first eight postoperative days, and bring it, as well as any remaining medication, to the postoperative visit for review. Remaining syringes will be assessed to determine the total number of doses of medication each patient received over the 8 day postoperative period.

All participating children and their parents will be advised to see medical evaluation emergently should a bleeding event occur, as is currently standard practice after adenotonsillectomy. All children with evidence of a bleed, such as a history of bleeding, active bleeding, or an oropharyngeal clot will be admitted, at least, for observation, at the discretion of participating surgeons. A large bore IV will be placed and IV fluids administered. Children with active bleeding or a large oropharyngeal clot will return to the operating room, at the discretion of the participating clinician, for control of hemorrhage under general anesthesia and endotracheal intubation. They will be instructed to discontinue the study drug, and take acetaminophen 15mg/kg (maximum dose 650mg) every 4-6 hours for pain control. Children prescribed oxycodone for pain control postoperatively will be able to continue narcotics as well.

At the end of the 14 day postoperative period, a study physician or participating research nurse will contact patients' parents/guardians to question about postoperative bleeding events. In cases where bleeding occurred, the written and electronic hospital events will be evaluated for further information. Bleeding events will be classified according to the type of intervention taken.

6. List study endpoints: How will the approach described give you the answer(s) to the questions you are investigating?

Response: Pain control questionnaires for each postoperative day, as well as a 9 day supply of medication (36 doses) will be dispensed at discharge. Patient's caregivers will be asked to complete the questionnaire daily on the day of surgery and for the first eight postoperative days and bring it, as well as any remaining study medication, to the postoperative

visit for review. Remaining medication will be measured to assess the total number of doses of medication that the patient received during the study period.

All patients will be instructed to go to the emergency room if there is any evidence of a post-operative bleed for evaluation and treatment. Data collection will be performed by participating surgeons and the research nurse. He/she will contact the parents of patients at the end of the 14-day postoperative period. If an episode of bleeding occurs, the caller will review any pertinent emergency room, outpatient, inpatient and operating room records for further information regarding the nature of the bleed and required treatment. Admission for observation and/or return to the operating room for hemorrhage control will be recorded.

Postoperative hemorrhage will be defined as any history of bleeding, mild or severe, occurring in the 14-day postoperative period. Postoperative hemorrhage will be defined as primary (occurring <24 hours after surgery) and secondary (occurring >/= 24 hours after surgery). For each category, postoperative hemorrhage will be stratified into three levels of severity:

- Level 1: children with any history of postoperative bleeding whether or not there was clinical evidence of bleeding. This level includes all children with a history of postoperative bleeding who were evaluated and/or treated by a physician in the emergency room, inpatient unit or operating room.
- Level 2: represents all children who required inpatient admission for postoperative hemorrhage regardless of the need for operative intervention. This level of severity excludes children evaluated in the emergency room for reported postoperative hemorrhage who had no clinical evidence of hemorrhage or clot and were deemed safe for discharge.
- Level 3: children who required admission and return to the operating room for control of post-tonsillectomy hemorrhage.

7. Inclusion Criteria: List all inclusion criteria. Clearly describe how eligibility will be determined and by whom.

Response: Patients ages 2-18 undergoing tonsillectomy with or without adenoidectomy by electrocautery alone for sleep disordered breathing or infectious tonsillitis will be included. Patients with complex medical conditions and craniofacial abnormalities will be included. Informed consent and child assent will be required for enrollment.

8. Exclusion Criteria: List all exclusion criteria. Clearly describe how ineligibility will be determined and by whom.

Response: Patients with a known personal or family history of a bleeding disorder will be excluded. Patients with a history of asthma, kidney or liver problems will also be excluded. Patients with tonsillectomy or adenoidectomy performed using a cold knife technique, microdebrider, coblation or plasma knife. Patients on NSAIDs for other medical conditions, or

those who have taken NSAIDs within 1 week of surgery will be excluded. Patients with allergy to aspirin or other NSAIDs, acetaminophen, Red Dye #40 or Red Dye #33 will also be excluded. Pregnancy testing using urine beta-HCG will be performed on all children > 13 years of age, or those younger than 13 who are menstruating; this is the testing protocol used at the Children's Hospital of Boston. Patients found to be pregnant will be excluded from participation.

9. Study Population: Specify characteristics of the study population (gender, age range, health status). State the target enrollment for a multi site trial here and describe any site specific restrictions, e.g. "Enrollment at MEEI will be limited to an age range of 18-45 although the sponsor's protocol allows an age range of 5-45."

Response: Males and females between the ages of 2 and 18 years undergoing tonsillectomy with or without adenoidectomy by electrocautery alone for sleep disordered breathing or infectious tonsillitis. The total target enrollment for all participating study sites is 722 (366 patients per arm).

A. How many potential subjects do you have access to for this protocol? Specify the anticipated screening sample size at MEEI and the probable duration of this study.

Response: Over the last 2 years, the average number of tonsillectomies for each contributing attending was 200. The anticipated screen sample size at MEEI is 600 annually, and that roughly 200 participants will sign-up to participate per year. We project that each participating institution will contribute 200 study subjects per year, and that it will take approximately 2 years to reach our target enrollment of 722. We plan to apply for Continuing Review until we reach target enrollment, should this taken longer than 2 years.

B. How many subjects would you need to recruit at MEEI to meet your target enrollment within the indicated time period for this study?

Response: 400

C. Provide statistical justification of sample size. Include a statement about the statistical power of the study to test the major hypothesis.

Response: In Dr. Gallagher and Dr. Hartnick's study of the use of dexamethasone and the risk of postoperative bleeding (in press), 137 children received dexamethasone and postoperative tylenol, and there were three type 3 bleeds requiring return to the operating room for control of hemorrhage, giving a roughly 2% type 3 bleed rate. This is consistent with MEEI quality and outcomes data for 2005-2009, which demonstrated that 2.25% (SD 0.5) of tonsillectomies performed during the period required return to the OR (type 3 bleeding) for control of hemorrhage. Therefore, we calculated the sample size for the non-inferiority trial using a type 3

bleed rate of 2% as our predicted type 3 bleed rate for patients in the control (acetaminophen) arm. Our margin of inferiority was 3% between control and experimental groups. We then calculated our sample size into account taking into account a desire to perform 3 looks at the data (at approximately 10%, 50% and 100% enrollment) and a projected 5% loss to follow-up rate.

We then calculated a projected sample size using a group sequential two proportions non-inferiority method using East v 5.4.2 and O'Brien-Flemming stopping boundaries determined by means of the Lan-DeMets approach with the following parameters: an alpha of 0.025, power of 80%, 5% projected loss to follow up rate, control bleed rate of 2%, non-inferiority margin of 3%, and 3 anticipated looks at the data. We calculated our total enrollment will need to be 722 subjects (366 per arm), with interval looks at n= 102 and n= 362 patients.

D. Describe how data collected will be analyzed.

Response: We plan to initially analyze the crude association between ibuprofen and bleeding rate using simple, univariate analysis. We will then construct a multivariate logistic regression model including ibuprofen exposure, pain control, outcome, and potential confounding factors such as age, surgical indication, gender, and operating surgeon. Analysis will be performed using an intention to treat analysis. Impact of losses to follow-up will be assessed using sensitivity analysis. Statistical analysis and data management will be performed using STATA, SAS and Microsoft Excel.

1. At the enrollment of 102, 362 and 722 participants, the study will be unblinded and data reviewed using both univariate and multivariate analysis.
    a. A simple, uni-variate analysis will be performed to evaluate the association between ibuprofen and bleeding (we are primarily interested in evaluating the association between ibuprofen and type 3 bleeding).
        i. The null hypothesis (ibuprofen does not increase the risk of type 3 postoperative hemorrhage) will be rejected if there is a greater than 3% increase, which is the preset equivalence margin, in type 3 bleeding in the ibuprofen cohort in comparison to the acetaminophen cohort.
            1. Based on statistical analysis, P values will be significant in the following conditions:
                a. 1st look (n=102) if $p < 0.00001$
                b. 2nd look (n=362) if $p < 0.001525$
                c. Final look (n= 722, total enrollment) if $p<0.025$
    b. A multi-variate logistic regression model will be used to evaluate ibuprofen exposure, pain control, outcome and potential confounding factors such as narcotics use, age, surgical indication, gender, and operating surgeon.

10. Study Specific Procedures: Clearly list all procedures (interventions, tests, surveys, etc.) to be performed for research purposes.

Response:

1. Postoperative analgesia: For the first 8 postoperative days, children will be administered QID, weight based analgesia from medication provided by the inpatient pharmacy at MEEI. Medication will be administered from an amber colored bottle containing 36 dosages of weight based medication. Each bottle will specify the patient's name, medical record number, and instructions regarding the volume of medication to be measured and dispensed for each dosage. The volume of medication dispensed for each child will be manipulated with OraBlend solution such that the weight based dose of ibuprofen volume will equal the weight based dose of acetaminophen volume; both medications will be dosed QID. Surgeons, nursing staff, and patients and their families will be blinded regarding the type of medication administered (acetaminophen vs. ibuprofen). Acetaminophen will be given as 15mg/kg dosing (maximum dose 650mg) and ibuprofen will be given as 10mg/kg dosing (maximum dose 600mg). Children with breakthrough pain eligible for narcotics (based upon age, OSA status) will be given prescriptions for weight based doses of oxycodone 1mg/1mL elixir (0.05-0.1mg/kg every 4-6 hours) as well as prescribed this medication for breakthrough pain while inpatients. After 9 days, patients will be instructed to take acetaminophen 15mg/kg (max dose 650mg) every 4-6 hours as needed for breakthrough pain. They will be instructed not to use nonsteroidal anti-inflammatory drugs (NSAIDS) in the postoperative period (14 days).

2. Surveys: On the postoperative day and during the first 8 postoperative days, parents will be asked to complete a questionnaire about their child's pain control on a daily basis. The questionnaire used includes a validated questionnaire about postoperative pain control, as well as additional questions regarding postoperative pain control and return to normal diet and sleep patterns. These questionnaires have been used by previous studies evaluating the use if ibuprofen for post-tonsillectomy pain control. Parents will be asked to being this questionnaire to their postoperative visit for data collection and review.

3. Collection of post-operative hemorrhage data: All patients will be instructed to go to the emergency room if there is any evidence of a post-operative bleed for evaluation and treatment. Data collection will be performed by participating surgeons and the research nurse. He/she will contact the parents of patients at the end of the 14-day postoperative period. If an episode of bleeding occurs, the caller will review any pertinent emergency room, outpatient, inpatient and operating room records for further information regarding the nature of the bleed and required treatment. Admission for observation and/or return to the operating room for hemorrhage control will be recorded.

Postoperative hemorrhage will be defined as any history of bleeding, mild or severe, occurring in the 14-day postoperative period. Postoperative hemorrhage will be defined as primary (occurring <24 hours after surgery) and secondary (occurring >/= 24 hours after surgery). For each category, postoperative hemorrhage will be stratified into three levels of severity:

- Level 1: children with any history of postoperative bleeding whether or not there was clinical evidence of bleeding. This level includes all children with a history of postoperative bleeding who were evaluated and/or treated by a physician in the emergency room, inpatient unit or operating room.
- Level 2: represents all children who required inpatient admission for postoperative hemorrhage regardless of the need for operative intervention. This level of severity excludes children evaluated in the emergency room for reported postoperative hemorrhage who had no clinical evidence of hemorrhage or clot and were deemed safe for discharge.
- Level 3: children who required admission and return to the operating room for control of post-tonsillectomy hemorrhage.

11. Standard of Care Procedures: Clearly list all standard of care (standard therapy) procedures (interventions, tests, etc.) to be performed regardless of the subject's enrollment in the study, but that will be included in the research assessment.

Response: All females of child bearing potential shall undergo a pregnancy test prior to surgery, regardless of their participation in the study as part of standard clinic care at MEEI. All patients will be administered 15mg/kg (max dose 650mg) of acetaminophen preoperatively prior to arrival in the preoperative area and dexamethasone 0.5mg/kg IV (maximum dose of 8mg) or methylprednisolone (SoluMedrol) 2.5mg/kg IV (maximum dose of 40mg) in the operating room prior to surgical commencement, which is standard practice at MEEI. The standard method of tonsillectomy among participating surgeons will be extracapsular monopolar electrocautery with standard settings of 12 watts (fulgurate) using a spatula tip. Bleeding will be controlled with suction cautery on a setting of 12-18 watts (fulgurate). Adenoidectomy will be performed at 30 watts (fulgurate). Anesthetic technique, perioperative analgesia with narcotics, and post-operative care will remain equivalent between the two study arms. Antibiotics will not be administered in the perioperative period. Postoperative anti-emetic therapy will be standardized by all collaborating physicians using standardized order sets. All patients will be prescribed postoperative analgesia, and those eligible to receive narcotics will also be prescribed oxycodone elixir. Postoperative hemorrhage will be managed the same, regardless of study participation.

12. Alternatives: For studies offering treatment, what treatment alternatives are available outside of this research?

Response: None. Patients unwilling to enroll in the study will have the tonsillectomy with or without adenoidectomy performed and receive postoperative analgesia of acetaminophen with or without supplemental narcotic medication according to current practice standards.

13. Describe the Time Commitment for Each Subject, e.g. 2 hours per visit/5 visits/10 hours total. For complex studies, be specific for each portion of the study.

Response: ach subject will require 3 visits. An initial visit/consultation/preop, the day of surgery, and a post-operative visit 2-4 weeks after surgery. The initial visit would last approximately 45 minutes. The surgery, including anesthesia recovery time, would last approximately six hours, and the postoperative visit would be about 15 minutes in duration. This time commitment does not deviate from the commitment required for patients undergoing tonsillectomy who will not be participating in the study.

We approximate study participation will require a roughly 2 hour time commitment for each subject in addition to the time described above. This incorporates a 10 minute time commitment per day to complete study-related questionnaires regarding postoperative pain control, as well as 15 minutes for questionning about postoperative bleeding during both a phone survey at the end of a 14 day postoperative period, and 15 minutes at the time of the scheduled postoperative visit.

14. Cost of Participation: Clearly describe any costs to Subjects as part of this research, e.g. copay for standard of care procedures, parking, etc.

Response: Patients will be responsible for any fees associated with the scheduled procedure (i.e. co-pays, deductibles, etc.) as determined by their insurance.

15. Payments for Participation: Describe all payments and/or reimbursement subjects will receive during the study, e.g. travel reimbursement, stipend, etc. Include mechanism for payment, e.g. cash, check, gift, etc.

Response: Patients will not be paid or reimbursed for participation in this study.

16. Subject Safety: Describe explicitly the methods and procedures for ensuring subjects' safety. Provide objective criteria for removing a subject from the study, e.g. objective criteria for worsening disease/lack of improvement, and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Response: We propose to establish a data and safety monitoring board (DSMB). The board will receive notification each time a bleeding event occurs in a study patient. Bleed rate data will be examined on a bi-annual basis (every 6 months), or if the objective, type 3 bleed rate

exceeds 6% (three times the expected rate of 2% type 3 bleeding based on a review of the literature and MEEI quality and outcomes data) after enrollment of the first 100 subjects. The study will be terminated if the type 3 bleed rate in either arm exceeds greater than 6%. Interim data-analyses will also be performed after recruitment of 102 subjects, and after 50% recruitment (n=362). At the first look, if the type 3 hemorrhage rate for the ibuprofen cohort exceeds 3% above the tylenol group, which is the non-inferiority interval used for our statistical design, with $p<0.00001$, the study will be terminated. The study will be terminated at this point if the type 3 bleed rate exceeds 6% (7 type 3 bleeding events). At the second look (n=362), the study will be terminated if the type 3 hemorrhage rate for the ibuprofen group exceeds 3% above the tylenol group, with $p<0.001525$. The study will also be terminated at this point if over 22 type 3 bleeding events have occurred (>6% objective bleeding rate).

17. Subject Injury: Describe the medical treatment available if injury occurs. Where and from whom will treatment be obtained? Are there limits to the treatment available? Who will pay for this treatment? Will the subject be responsible for any costs for treatment, e.g. co-pay?

Response: Emergency treatment will be provided by Dr. Hartnick and the Co-Collaborators should a participant be injured as the result of participating in this study. Third party payers will be billed for any emergency services, when applicable and the participant will be responsible for any deductibles and co-payments required by the third party payer. There will be no compensation as the result of any injury.

All participating children and their parents will be advised to see medical evaluation emergently should a bleeding event occur, as is currently standard practice after adenotonsillectomy. All children with evidence of a bleed, such as a history of bleeding, active bleeding, or an oropharyngeal clot will be admitted, at least, for observation. A large bore IV will be placed and IV fluids administered. Children with active bleeding or a large oropharyngeal clot will return to the operating room, at the discretion of the participating clinician, for control of hemorrhage under general anesthesia and endotracheal intubation. They will be instructed to discontinue the study drug, and take acetaminophen 15mg/kg (maximum dose 650mg) every 4-6 hours for pain control. Children prescribed oxycodone for pain control postoperatively will be able to continue narcotics as well.

EXPECTED RISKS AND DISCOMFORTS

18. Describe any foreseeable risks and discomforts to subjects: Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. Include psychosocial risks and risks related to privacy and confidentiality. Describe risks to developing fetus or nursing infant if applicable.

Response: Tonsillectomy with or without adenoidectomy is not without risk. The following are potential risks of surgery that apply to both arms of the study: pain, postoperative hemorrhage, anesthetic and airway risks, aspiration, post-obstructive pulmonary edema, atlanto-axial subluxation, mandible fracture and dislocation, eustacian tube injury, injury to the lips, teeth, tongue and gums, dehydration, nasopharyngeal stenosis, and velopharyngeal insufficiency.

19. Describe how the risks to subjects will be minimized, i.e. using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk or, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Response: Risks to subjects will be minimized through the use of standardized operative procedure. All subjects will receive postoperative analgesia, either tylenol or ibuprofen, both of which have been proven effective analgesics after tonsillectomy. All subjects will be educated regarding signs and symptoms of postoperative hemorrhage and advised to seek emergency care should bleeding occur; this is also standard practice.

Data will be stored on a Microsoft Excel database which will be kept on a password protected server that the principal and associate investigators and research nurse can access to enter their data. No data will be stored with an associated patient name. Code sheets that link the subject number to patient name will be kept in a locked file on only one computer with a backup copy of the file stored in a locked cabinet in the principal investigator's office. The code sheets will be maintained by the principal and associate investigators, and the computer used to store the code will be different than that used to store the Excel database. Only study investigators will have access to the passwords. No data linked to a subject will be released without written permission from the subject.

EXPECTED BENEFITS

20. Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, e.g. "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, i.e. through increased knowledge of human physiology and behavior, improved safety or technological advances, etc.

Response: Tonsillectomy is the second most common surgery performed in the pediatric population. Knowledge gained by this trial will help to improve the safety of tonsillectomy, and potentially pain management after surgery, for hundreds of thousands of children each year. While meta-analysis of NSAID use after tonsillectomy has suggested NSAID use may not increase the risk of bleeding, further research is needed to evaluate specific NSAIDs and the timing of administration. Therefore, it is surprising that the American Academy of Otolaryngology would advocate the use of ibuprofen in the perioperative period when further

research is warranted. In Europe, administration of ibuprofen and other NSAIDs after tonsillectomy in the pediatric population is widely accepted, though members of the American otolaryngology community are more hesitant to use them due to the theoretical increased risk for bleeding. The results of this study would help to specifically address concerns regarding the use of ibuprofen in the postoperative period. The results of such a definitive study would possibly affect our standards of care, as well as both national and international norms.

RECRUITMENT METHODS

21. Describe a) when, b) where, and c) how potential subjects will be recruited, methods that will be used to identify potential subjects, and materials that will be used to recruit subjects, i.e. posters, phone scripts, letters, etc. Attach copies of posters, scripts, letters, etc., to be used for recruitment purposes to this application package.

Response: Participants will be recruited from the medical practices of Dr. Hartnick and his Co-Collaborators. Participants will be identified when they are scheduled for a tonsillectomy and approached to participate in this study. No other recruitment materials will be used.

EQUITABLE SUBJECT SELECTION

22. The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, i.e. men, women, pregnant women, children and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Response: All subjects who meet inclusion criteria will be recruited by the P.I. from patients already scheduled for tonsillectoy and therefore all have an equal chance of participating in this study. Subjects meeting any exclusion criteria will not be included.

23. Provide justification for involving vulnerable subjects and fill out the relevant supplemental form.

[]Adults unable to consent (fill out supplemental form IX)

[X] Individuals who are not yet adults (infants, children, teenagers) (fill out supplemental form XII)

[X] Pregnant women/females of childbearing potential (fill out supplemental form XI)

[] Prisoners (check with our office for specific form)

[] Employees, study staff, students, residents, fellows (describe safeguards provisions)

[X] Non-English Speaking (answer questions 24 & 28)

24. If non-English speaking subjects are to be excluded from participation in the research, please provide a scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research solely due to language.

Response: NA

INFORMED CONSENT PROCESS

25. Explain in detail a) how, b) when, c) where, and d) by whom consent is obtained. Describe the timing of consent, i.e. how long subjects will be given to consider participation. For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent.

Response: The study will be introduced to the patients and his or her family at time the tonsillectomy is scheduled. The Principal Investigator of each participating site will introduce the study and answer any questions patients and their families may have. They will be given the opportunity to consider participation until prior to arrival in the preoperative area. Those who do not sign an ICF will not be included in the study.

26. When subjects are to be enrolled from among the investigators' own patients or MEEI employees describe how potential for coercion will be avoided.

Response: All enrolled subjects will be patients who are already scheduled for a tonsillectomy. They will be informed that non-participation in the study will not affect the surgery already schedule. Thus, there will be no potential for coercion**.**

27. For research involving minors, please explain how parental permission and child assent will be obtained.

Response: Participation in the study will be introduced prior to surgery to both patent and child. Consent and assent (for eligible age appropriate children and if necessary per clinical site) will be signed prior to the surgery.

28. For research involving non-English speaking subjects, specify potential languages and explain how consent will be obtained (e.g. use of MEEI Interpreter Services and/or translated consent forms).

Response: For subjects involving non-English speaking subjects, MEEI Interpreter Services will be utilized.

DATA/SAFETY MONITORING PLAN

29. Describe plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. This plan should include a description of the safety and/or efficacy data that will be reviewed, the planned frequency of review, and who will be responsible for this review and for determining whether the research should be altered or stopped. Describe any stopping rules for the study, when appropriate. Depending upon the risk level, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

Note: Regardless of data and safety monitoring plans by the sponsor or others, the Principal Investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Response: We propose to establish a data and safety monitoring board (DSMB). The board will receive notification each time a bleeding event occurs in a study patient. Bleed rate data will be examined on a bi-annual basis (every 6 months), or if the objective, type 3 bleed rate exceeds 9.3% (1 SD above the mean bleed rate for tonsillectomy) after enrollment of the first 100 patients at MEEI. The study will be terminated if the type 3 bleed rate in either arm exceeds greater than 6%. Interim data-analyses will also be performed after recruitment of 102 subjects, and after 50% recruitment (n=362). At the first look, if the type 3 hemorrhage rate for the ibuprofen cohort exceeds 3% above the tylenol group, which is the non-inferiority interval used for our statistical design, with $p<0.00001$, the study will be terminated. The study will be terminated at this point if the type 3 bleed rate exceeds 6% (7 type 3 bleeding events). At the second look (n=362), the study will be terminated if the type 3 hemorrhage rate for the ibuprofen group exceeds 3% above the tylenol group, with $p<0.001525$. The study will also be terminated at this point if over 22 type 3 bleeding events have occurred (>6% objective bleeding rate). Dr. Stacey Gray, Dr. Maynard Hansen and Dr. Mark Volk have been recruited to serve as the DSMB for this study.

30. Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports.

Response: At the end of a 14-day postoperative period, all subjects will be interviewed regarding any bleeding events. In the case of bleeding, review of the electronic record will be performed to further investigate the severity of bleeding and the interventions taken to control hemorrhage. The DSMB will be notified each time a bleeding event occurs in a study patient. Bleed rate data will be examined on a bi-annual basis (every 6 months), or if the objective, type 3 bleed rate exceeds 6% (three times the mean type 3 bleed rate for tonsillectomy based on review of the literature and MEEI quality and outcomes data) after enrollment of the first 100 patients at MEEI. The study will be terminated if the type 3 bleed rate in either arm exceeds greater than 6%. Interim data-analyses will also be performed after recruitment of 102 subjects, and after 50% recruitment (n=362). At the first look, if the type 3 hemorrhage rate for the ibuprofen cohort

exceeds 3% above the tylenol group, which is the non-inferiority interval used for our statistical design, with $p<0.00001$, the study will be terminated. The study will be terminated at this point if the type 3 bleed rate exceeds 6% (7 type 3 bleeding events). At the second look (n=362), the study will be terminated if the type 3 hemorrhage rate for the ibuprofen group exceeds 3% above the tylenol group, with $p<0.001525$. The study will also be terminated at this point if over 22 type 3 bleeding events have occurred (>6% objective bleeding rate).

31. When the Principal Investigator is also the regulatory sponsor of the IND/IDE, include the plan for identifying, reviewing and, when applicable, sharing adverse events with investigators at other sites. Specify the time frame.

Note: In addition to the adverse event reporting requirements to the sponsor of FDA, the principal investigator must follow the Human Studies Committee Policy for Reporting Adverse Events and Unanticipated Problems.

Response: NA

QUALITY ASSURANCE

32. Describe your process to ensure that all persons assisting with the trial are sufficiently knowledgeable *about the protocol*, the investigational product(s), and their trial-related duties and functions. Please do not include CITI training, as this is a requirement for doing human subjects research and is not specific to your protocol.

Response: All study personnel will be required to be familiar with the study protocol and previous research involving nonsteroidal anti-inflammatory use after tonsillectomy. A procedure manual, outlining subject recruitment, consent and assent procedures, postoperative management, data aquisition and recording will be drafted, an all study participants will be required to be familiar with and follow these procedures.

33. Describe the plan to be followed by the Principal Investigator/study staff to monitor the validity and integrity of the data and adherence to the IRB-approved protocol.

Response: The principal investigators at each participating site will review all current data at the site on a semi-annual basis to ensure accuracy and adherence to study protocol. Should he find any discrepancy in the data, he will review the study protocol with all study staff involved, and retrain and remediate as necessary.

34. Specify who will be responsible for monitoring and the planned frequency of monitoring, i.e. who will review the accuracy and completeness of case report form entries, source documents and informed consent.

Response: The Principal Investigators at each participating site will be responsible for monitoring and the planned frequency of monitoring the data.

CONFIDENTIALITY

35. Check all patient identifiers collected for this study that will be recorded with or linked by code to the data. If any categories are checked, you will need to obtain HIPAA authorization from the subject or a waiver of HIPAA authorization from the HSC to perform research.

[]None of the listed identifiers will be recorded as part of the study

[X] Name [] Telephone Number

[] Social Security Number [] Fax Number

[X] Medical Record Number [] Email Address

[]Address by Street Location []Web URL's

[]Address by Town/City/Zip Code []Internet Protocol (IP) Address

[]Health Plan Beneficiary Number []Account Number

[]Certificate/License Number []Ages Over 89

[]Full Face Photographic Image

X[]Elements of Dates (Admission/Discharge Date, Procedure Date, Date of Birth or Death)

[]Vehicle ID Number and Serial Number Including License Plate Number

[]Medical Device Identifiers and Serial Number

[]Biometric Identifiers (e.g. fingers or voice prints)

[]Other unique identifiers or code that can be used to identify the participant

36. If you selected "Other" please explain:

Response:

37. Describe the methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers, removing face sheets or other identifiers from completed surveys and/or questionnaires, proper disposal of printed computer data, limited access to study data, use of password-protected computer databases, training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

Note: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as genetic, sexual, or criminal.

Response: Study-related PHI will be maintained on a shared server (T drive) to allow for back up and more protection against data breach. Access will be limited to authorized study staff through password protection. Published data will not have any personal identification attached.

38. How long will data be retained, i.e. when and how link to identifiable data be destroyed?

Response: As mentioned above any study-related PHI will be kept on shared server (T drive). Once the study has completed, all identifiable data that was collected will be kept according to MEEI guidelines or de-identified according to HSC recommendations.

39. For specimens or data being sent to other institutions, please indicate to whom the specimens or data will be sent, and what specific identifiers (per question 35) will be sent.

Response: NA

40. Will specimens/data be stored at outside sites for future use not described in the protocol? Will subjects be able to withdraw their specimens/data and, if so, how would they do so? When appropriate, submit documentation of IRB approval from the recipient institution.

Response: NA

41. When specimens or data collected by researchers outside MEEI will be sent to MEEI investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

Response: Data collected from other participating institutions will be entered into excel files in a deidentified fashion before they are shared with the investigators at MEEI. Other participating institutions will also require their own IRB approval, DSMB, and all questionnaire and consent/assent forms will also be approved by those institutions.

42. Provide any additional information you feel is important for the Committee to know about your project.

Response:

43. INVESTIGATOR- INITIATED STUDIES
This section should be completed by the PI for investigator-initiated projects that have not been peer-reviewed by sponsoring agencies. The checklist below is designed to assist the PI in developing a project that meets peer-review standards of scientific design, including appropriate scientific rationale, study endpoints, biostatistical justification, and recruitment goals.

Please check the boxes below to indicate these topics have been covered in detail in this application.

[X]**Preliminary data from the literature (or from your own previous studies)**
[X]**Specific aims and corresponding hypotheses**
[X]**How the question or hypothesis being tested will contribute important knowledge to the field**
X[]**The primary outcome (and secondary outcomes as appropriate)**
[X]**Justification that the study design is appropriate for answering the study hypothesis**
[X]**Justification that the study is powered and controlled (sample size, appropriate control (s), adequate plan for statistical analysis) for this purpose**

COVER PAGE

Clinical Protocol Title: Postoperative Ibuprofen and the Risk of Bleeding After Tonsillectomy with or without Adenoidectomy

HSC #: 11-054H

IRBNet ID: 242942
Clinical trials.gov number: NCT01605903

Version 6 6/01/16
Phase of clinical investigation: Phase 1

Sites of Investigation:
Massachusetts Eye and Ear Infirmary; Boston, MA

Madigan Army Base; Tacoma, WA

Naval Medical Center of San Diego, Department of Otolaryngology; San Diego, CA

Naval Medical Center, Department of Otolaryngology, Portsmouth, VA

Brooke Army Medical Center, San Antonio, TX

IND/IDE number: NA
Investigational drug(s) or device(s): NA

Regulatory Sponsor:
Christopher Hartnick, MD
Department of Otolargyngology
Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114

Funding Sponsor: Intradepartmental funding at MEEI, US Army and Navy at other sites.

Study Monitor:
Data Safety and Monitoring Board for MEEI Site: Dr. Stacey Gray (MEEI), Dr. Maynard Hansen (MEEI/NWH), Dr. Mark Volk (CHB)

Medical Director:
Christopher Hartnick, MD
Department of Otolargynology
Massachusetts Eye and Ear Infirmary

243 Charles Street

Boston, MA 02478

617-573-4206

MEEI:

Principal Investigator: Christopher Hartnick, MD

CoInvestigators: Donald Keamy, MD; Michael Cohen, MD; Gillian Diercks, MD; Jennifer Setlur, MD; Jill Comins, NP; Sarah Bowe, MD

Department of Otolaryngology

Massachusetts Eye and Ear Infirmary

243 Charles Street

Boston, MA 02478

617-573-4206

Madigan Army Hospital

Principal Investigator: Mark Boseley, MD, MS Epi

CoInvestigator: Brian Chen, MD, CPT, MC; Derek Rogers, MD

Department of Otolaryngology

Madigan Army Medical Center

Madigan Army Medical Center

BLDG 9040A Jackson Ave

Tacoma, WA 98431-1100

San Diego Naval Hospital

Principal Investigator: LCDR Matthew Brigger, MD, MPH (ended 1/1/16); Philip Gaudreau, MD (started 1/1/16)

CoInvestigators: LT Colleen Perez, MD; Cheryl McNeal BS, CRC.

Department of Otolaryngology

Naval Medical Center

3460 Bob Wilson Drive, Suite 200

San Diego, CA 92134-2200

Portsmouth Naval Hospital

Principal Investigator: Thomas Gallagher, DO

Co-Investigator: Jonathan Melzer, MD

Department of Otolaryngology

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620 John Paul Jones Circle

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Brooke Army Medical Center

Principal Investigator: Stephen Maturo, MD

Department of Otolaryngology

Brooke Army Medical Center

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Massachusetts Eye and Ear Infirmary

SUPP M - Clinical Trial Template

STUDY DESIGN SCHEMATIC

RECRUITMENT

MEEI: Drs. Hartnick, Keamy, Cohen, Setlur, Diercks (starting 9/1/16)

Approximately 250 patients/year

Drs. Boseley and Rogers (Madigan Army Base, Tacoma, WA)

Drs. Brigger and Gaudreau (Naval Medical Center, San Deigo, CA)

Dr. Gallagher (Naval Medical Center, Portsmouth, VA)

Dr. Maturo (Brooke Army Medical Center, San Antonio, TX)

Approximately 400 patients/year

Inclusion Criteria

Patients ages 2-18

Tonsillectomy with or without adenoidectomy for recurrent tonsillitis or SDB

Performed by electrocautery alone

Exclusion Criteria

Known personal/family h/o bleeding disorder

Asthma, kidney or liver problems

Cold knife, microdebrider, plasma blade, coblation technique

On NSAIDs for other conditions or if NSAIDs taking within 1 week of surgery

Taking steroids

Allergy to ASA, NSAIDs, acetaminophen, Red Dyes

INTERVENTION

Receive acetaminphen 15mg/kg (max dose 650mg) preop

Receive dexamethasone 0.5mg/kg (max dose 8mg) in OR

No antibiotics administered

Extracapsular tonsillectomy performed with electrocautery (12 watt), adenoidectomy performed with suction cautery (30 watt), hemostatis with suction cautery (12-18 watt)

Randomized

Ibuprofen 100mg/5mL (Leader®); 10mg/kg (max dose 600mg) po QID x 8 days to start 4 hours after preop acetaminophen dose.

Acetaminophen 160mg/5mL (Leader®); 15mg/kg (max dose 650mg) po QID x 8 days to start 4 hours after preop acetaminophen dose.

9 daily postoperative pain questionnaires and medication dosing records.

+

Oxycodone 1mg/1mL, 0.05-0.1mg/kg if elibile

DATA ACQUISITION

Bleeding Questionnaire performed at the postoperative visit

Dosing/Pain Questionnaires , Left-over medication collected at the Postoperative Visit

Bleed Categories

Primary (within 24 hours) or Secondary

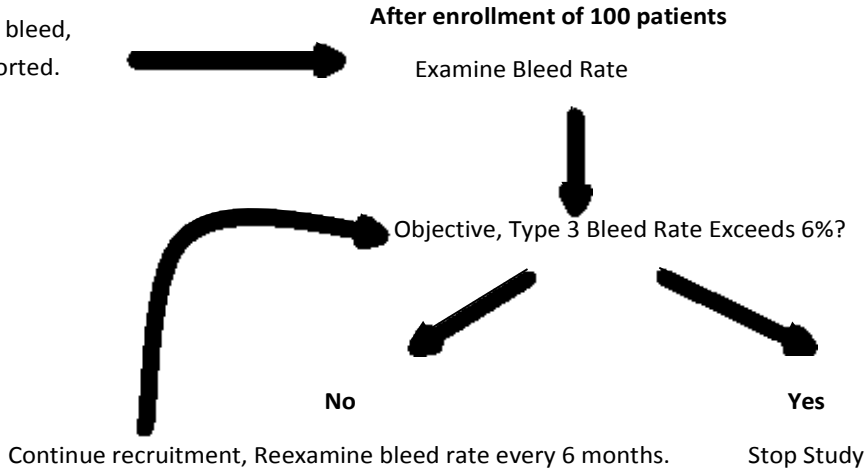
+

Type 1: History of Postoperative Bleeding, No intervention.

Type 2: History of Bleeding, Admitted for Observation.

SAFETY MONITORING

DSMB notified each time there is a study patient bleed, total number of bleeds and total enrollment reported.



STATISTICAL ANALYSIS

First Look: Unblind study at n=102. If 3% difference between groups for Type 3 bleeding with $p<0.00001$, or >7 type 3 bleeds (> 6% of study population), terminate Study. Otherwise continue.

Second Look: Unblined study at n=362 (halfway point). If 3% difference between groups for Type 3 bleeding with $p<0.001525$, or > 22 type 3 bleeds (>6% of study population), terminate Study. Otherwise continue.

Final Look: Stop enrollment at n= 722 and unblind study. If 3% difference or more between study groups, $p<0.025$, the difference is significant.

1. CLINICAL PROTOCOL

1.1 Background

Tonsillectomy with and without adenoidectomy is one of the most commonly performed surgical procedures in the pediatric population. The incidence of adenotonsillectomy has increased over the past four decades (1). This is mainly due to increased awareness of the potential adverse consequences that pediatric sleep disordered breathing (SDB) may have on development and long-term pulmonary and cardiovascular health. SDB has surpassed recurrent tonsillitis as the most common indication for adenotonsillectomy in children (2-5). Over the past decade, according to the CDC's National Health Statistic Report on ambulatory surgery performed in the US, annual rates of tonsillectomy performed with and without adenoidectomy in children aged 15 and younger increased from 287,000 to 530,000 (6, 7). Adenotonsillectomy is the second most common procedure performed on children under the age of 15. Although generally considered a safe procedure, adenotonsillectomy has significant morbidity and potential for complications, particularly in the pediatric population. Complications include postoperative hemorrhage, dehydration, pain, anesthetic complications and airway risks, aspiration, and post-obstructive pulmonary edema (8). In young children, the risk of adenotonsillectomy is more critical due to smaller airways and respiratory reserve, as well as smaller blood volume (5).

Postoperative bleeding can be categorized as a primary event, occurring < 24 hours after surgery, or a secondary event, occurring >24 hours after tonsillectomy. Additionally, events can be further described by the interventions taken, such as emergency room visits, admission for observation, or return to the operating room to achieve hemostasis. Postoperative bleeding rates, including both primary and secondary events, range from 3.3-20%, with a mean of 4.5% (9). Thus, annually, tens of thousands of children experience exposure to potentially life-threatening postoperative hemorrhage, often requiring readmission, anesthetic exposure, and operative control of hemorrhage.

Postoperative pain contributes significantly to post-tonsillectomy morbidity. While narcotics are effective in controlling postoperative pain, they are often contraindicated, particularly in children with sleep disordered breathing, because of their potentially adverse side effects on respiration and the central nervous system (10). Nonsteroidal anti-inflammatories (NSAIDS), which block prostaglandin-induced inflammation and edema, are an attractive therapeutic option because they do not result in respiratory and central nervous system depression, and therefore may reduce the risk of postoperative respiratory depression, nausea and vomiting, excessive sedation and urinary retention. NSAIDS have been shown to be effective analgesics after tonsillectomy (11,12). However, because their mechanism of action may also interfere with platelet aggregation and increase bleeding time, their use is balanced with concern about an increased risk of postoperative hemorrhage. Aspirin, which irreversibly inhibits cyclooxygenase, affects coagulation and bleeding for up to 10 days, has been associated

with an increased bleed rate after tonsillectomy (13). However, non-aspirin NSAIDs demonstrate a reversible inhibition of COX-1 and COX-2, and therefore do not have the same severe, prolonged effects on bleeding (14). Ibuprofen, a derivative of propionic acid, is widely used for musculoskeletal pain, but the study of its use for post-tonsillectomy analgesia is limited.

In 2011, The American Academy of Otolaryngology published Clinical Practice Guidelines outlining evidence-based selection and perioperative management strategies for tonsillectomy in children. As part of a recommendation that clinicians educate caregivers about the importance of postoperative pain management, Baugh et al advocated the use of ibuprofen postoperatively, stating, "ibuprofen can be used safely for pain control after surgery" (15), citing a 2005 Cochrane Review of NSAIDs and post-tonsillectomy bleeding in support of this guideline (16). The Cochrane Review recently added additional studies to their analysis and results remained similar. The most recent Cochrane Review, published in 2010, evaluated 15 randomized trials comparing NSAIDs with other analgesics or placebo, and determined that NSAID use did not significantly alter the number of perioperative bleeding episodes, both requiring and not requiring surgical intervention; this review did not distinguish between primary and secondary bleeding events (17). Because post-tonsillectomy hemorrhage is an uncommon event, a large number of participants is required to provide an adequate number of events to give a significant result, therefore the large sample size of >1000 children in the Cochrane Review is admirable. However, sample sizes were not adequate to compare the risk of bleeding with each individual NSAID. Additionally, NSAIDs were given in both oral and parenteral forms, as well as preoperatively, intraoperatively and postoperatively, and the duration of postoperative analgesic use differed between studies. The surgical technique used was not uniform between studies as well. It is our feeling that because of these limitations, the data is not sufficient to broadly implement the Academy's recommendation that ibuprofen can be safely used for post-tonsillectomy analgesia without more carefully controlled, prospective study.

Although there are many studies in the literature evaluating NSAID use after tonsillectomy, there are few randomized-prospective trials evaluating the use of ibuprofen, and few trials are powered to adequately assess the risk of postoperative hemorrhage. Designing and executing a study to specifically evaluate ibuprofen after pediatric tonsillectomy and rates of post-operative hemorrhage requiring return to the operating room for control is important to the pediatric otolaryngology community, particularly given the American Academy of Otolaryngology's recent clinical guidelines. The results of such a definitive study would possibly affect the tens of thousands of children at risk for post-tonsillectomy hemorrhage every year. It would affect our own standards of care as well as national and international norms.

Preliminary Studies:

At the Massachusetts Eye and Ear Infirmary there is no precedent for administering ibuprofen to children after tonsillectomy with or without adenoidectomy. Despite American Academy of Otolaryngology support for the use of ibuprofen in the postoperative setting,

pediatric otolaryngologists at our institution are still hesitant to administer ibuprofen postoperatively without additional study of its use.

Within the Department of Pediatric Otolaryngology at the Massachusetts Eye and Ear Infirmary there is a precedent for successful completion of randomized, controlled trials involving adenotonsillectomy (19, 20). With principal investigators dedicated to clinical research, as well as research nurses and coordinators at our disposal, a prospective, controlled clinical trial of ibuprofen use after tonsillectomy can be implemented. Additionally, the Massachusetts Eye and Ear Infirmary calculates annual post-tonsillectomy hemorrhage rates, including percentage of patients returning to the emergency room for evaluation for possible post-operative bleeding, as well as the percentage of patients returning to the operating room for control of bleeding. Thus, there is a precedent for collecting data on postoperative bleeding events, as well as a controlled bleed rate to which prospective study hemorrhage rates can be compared.

The goal of our study is to determine if postoperative ibuprofen affects the rate of post-tonsillectomy hemorrhage using a non-inferiority trial design, which is intended to show that the effect of ibuprofen is no worse than acetaminophen, which will serve as our control. This differs from an equivalence trial, which aims to demonstrate that the experimental and control group do not differ more than a specified amount. The equivalence margin set for non-inferiority trials is often smaller than the treatment difference for which a placebo-controlled trial is powered, requiring a larger sample size. This will address two issues we have with the current literature evaluating NSAID use after tonsillectomy: inadequate sample size and unrealistic treatment differences, including up to a 20% difference in bleed rates, required to detect a significant difference between NSAID and control groups. Because our trial will be designed to test non-inferiority, the null hypothesis will assume inferiority: the objective, type 3 bleed rate in patients treated with postoperative ibuprofen after tonsillectomy will be increased compared to the rate in patients given acetaminophen.

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1.2 Rationale

Nonsteroidal anti-inflammatories (NSAIDs) block prostaglandin-induced inflammation and edema. They are an attractive alternative to narcotic analgesics because they do not cause respiratory or central nervous system depression. NSAIDs previously have been shown to be effective for the control of post-tonsillectomy pain. However, because of reversible COX-1 and COX-2 inhibition, there is concern that ibuprofen and other NSAIDs may temporarily inhibit platelet aggregation and increase risk of bleeding postoperatively. A recently published Cochrane metaanalysis demonstrated there is no increased risk of postoperative hemorrhage, however, and the American Academy of Otolaryngology has endorsed the use of ibuprofen as an analgesic in patients undergoing adenotonsillectomy. Ibuprofen is used widely in the pediatric population, both for treatment of musculoskeletal pain as well as an anti-pyretic. Ibuprofen is an NSAID formulation that is commonly used and widely available, domestically here in the US as well as internationally.

For this study, we feel it is important to evaluate the effect of ibuprofen on post-tonsillectomy hemorrhage and pain control by dosing the drug in a similar way to how it would be used in the community. Other studies of NSAIDs and tonsillectomy gave investigational drugs parenterally, or in one to two doses in the immediate postoperative period. Therefore, we do not feel the results of these previous studies can be generalized to the effects of NSAID use throughout the postoperative period. The highest risk of bleeding after tonsillectomy is roughly 1 week from surgery, and we are interested in evaluating how NSAID use during this time period may affect bleeding risk as well. Additionally, previous studies have shown that significant postoperative pain extends up to 8 days after surgery. Therefore, we have designed to study so that ibuprofen is taken orally at the maximum dose, just as acetaminophen is often maximally dosed in the postoperative period in these patients, 10mg/kg, and for 9 days (the day of surgery and eight postoperative days).

This study will evaluate the effects of ibuprofen on postoperative bleeding and pain in children aged 2-18 years. Children undergoing tonsillectomy with or without adenoidectomy with electrocautery for recurrent tonsillitis and sleep disordered breathing/OSA will be eligible to participate. We will exclude children with NSAID or aspirin allergy, acetaminophen allergy (our control), bleeding disorders, asthma, lung, kidney or liver disease, or allergy to the dyes used in the medications used.

2. STUDY OBJECTIVES

2.1 Primary Objective

Aim 1: To compare the rates of post-tonsillectomy bleeding between pediatric patients who receive postoperative ibuprofen to those who receive acetaminophen in a prospective, randomized, blinded and controlled trial.

The primary objective of this study is to determine if postoperative ibuprofen at 10mg/kg dosed QID (four times daily, roughly Q6 hours) postoperatively for 9 days is associated with an increased rate of post-tonsillectomy bleeding requiring operative intervention for hemostasis in children when compared with acetaminophen. To achieve this, rates of post-tonsillectomy bleeding, both primary, defined as occurring < 24 hours after surgery, and secondary, defined as occurring > 24 hours after tonsillectomy, will be recorded. Additionally, distinction will be made between bleeds requiring emergency room evaluation, admission for observation, and operative control of hemorrhage.

2.2 Secondary Objective(s)

Aim 2: To compare the rates of post-tonsillectomy hemorrhage when studying different groups of patients based upon their age, indication for tonsillectomy, or operating surgeon.

The second objective of this study is to determine if bleeding rates differ according to surgical indication, age of the patient, or operating surgeon, using a multi-variate logistic regression model. This is important since indication for tonsillectomy varies in children. Younger children tend to undergo tonsillectomy for obstructive sleep symptoms whereas older children tend to undergo tonsillectomy for infectious tonsillitis.

Aim 3: To evaluate effectiveness of ibuprofen as a post-tonsillectomy analgesic in comparison to Acetaminophen, which is currently the standard of care at our institution.

The third objective of this study is to evaluate the efficacy of ibuprofen at 10mg/kg dosing (max dose 600mg) at QID dosing as an analgesic in the postoperative period in comparison to Acetaminophen, 15mg/kg (max dose 650mg), which is currently the standard of care at our institution. Previous studies have determined that ibuprofen at 5mg/kg dosing is an effective post-tonsillectomy analgesic, however 10mg/kg dosing, the maximum ibuprofen dose, has not been previously evaluated in the literature. We feel it is important to evaluate both the analgesic effect and rate of post-tonsillectomy bleeding associated with this maximum dosing if ibuprofen is to be widely used in the postoperative period after tonsillectomy.

3. STUDY DESIGN

3.1 Study Design Description

Recruitment: Patients will be recruited from the practices of Drs. Hartnick, Keamy, Setlur, and Cohen and Diercks (starting 9/1/16) (The Massachusetts Eye and Ear Infirmary), as well as Drs. Boseley and Rogers (Madigan Army Base; Tacoma, WA), Brigger and Gaudreau (Naval Medical Center of San Diego, Department of Otolaryngology; San Diego, CA), Maturo (Brooke Army Medical Center, Department of Otolaryngology; San Antonio, TX), and Gallagher (Naval Medical Center, Department of Otolaryngology; Portsmouth, VA). Over the last two years, the average annual number of pediatric tonsillectomies for each collaborating investigator was approximately 200. Informed consent will be obtained for the study by the principal investigator, co-investigators, or research nurses at the time of the preoperative visit or on the day of surgery prior to arrival in the preoperative area.

Inclusion criteria: Patients ages 2-18 undergoing tonsillectomy with or without adenoidectomy by electrocautery alone for sleep disordered breathing or infectious tonsillitis. Patients with complex medical conditions and craniofacial abnormalities will be included. Only patients who are not pregnant will be included. Informed consent and child assent will be required for enrollment.

Exclusion criteria: Patients with a known personal or family history of a bleeding disorder will be excluded. Patients with a history of asthma, kidney or liver problems will also be excluded. Patients with tonsillectomy or adenoidectomy performed using a cold knife technique, microdebrider, coblation or plasma knife. Patients on NSAIDs for other medical conditions, or those who have taken NSAIDs within 1 week of surgery will be excluded. Patients with allergy to aspirin or other NSAIDs, acetaminophen, Red Dye #40 or Red Dye #33 will also be excluded. Patients on oral steroids will be excluded. Pregnancy testing using urine beta-HCG will be performed on all children > 13 years of age, or those younger than 13 who are menstruating. Patients found to be pregnant will be excluded from participation. Patients and parents who are unable to understand study instructions will be excluded. Patients unwilling to enroll in the study will have the tonsillectomy with or without adenoidectomy performed according to current practice standards.

Randomization: Patients will be randomized upon enrollment after obtaining informed consent, and assent when indicated. Randomization will be performed centrally by the Massachusetts Eye and Ear Infirmary pharmacy, and groups of randomization schemes will be distributed to the pharmacies of participating institutions. The MEEI pharmacy randomization scheme will occur via a one-to-one scheme generated based on a uniform (1, 2) random number generator using “Research Randomizer,” which is available online at

www.randomizer.org. 722 random number assignments were generated based on an anticipated n = 722. So far, MEEI has been assigned numbers 1-400, San Diego is assigned 401-500, and Madigan is assigned numbers 601-700. *Initially Madigan had received numbers 501-600, however prior to enrollment there was a breach in blinding of this scheme, so the study numbers were thrown out and additional numbers were dispensed to the site.*

Blinding: The surgeon, nurses, and patient/parent will be blinded regarding to which arm the patient has been randomized. The pharmacy of each institution will dispense grape-flavored ibuprofen 100mg/5mL (Leader→) or grape-flavored acetaminophen 160mg/5mL (Leader→) based upon the arm to which each participant has been randomized. Ibuprofen will be dosed at 10mg/kg (max dose 600mg) and acetaminophen at 15mg/kg (max dose 650mg), dosing for each will be QID (roughly Q6 hours, however we left dosing QID to allow for some flexibility in the dosing schedule to accommodate patient sleeping schedules). The pharmacy will manipulate the volume of each medication using Ora Blend suspension so that for each child, weight based dosing of each medication will be equivalent in volume. Volume manipulation tables are provided in Appendix A. For each child, an amber colored bottle of 36 doses of study medication will be prepared. The bottle will indicate the patient's name, medical record number, and the volume to be given for each dose of medication. The first dose of study medication will be dispensed 4 hours after the preoperative acetaminophen dose. Thereafter, medication will be dosed QID (or roughly 6 hours apart).

At Portsmouth, San Diego and MEEI Sites: nursing staff will draw up study medication in study supplied amber colored syringes from the bottle of study medication. Upon discharge, the patients will be discharged with remaining medication in the bottle, as well as 2 amber colored syringes to draw up medication at home.

At Madigan: Due to nursing regulations, nurses at this institution are not authorized to draw up study medication. At this institution, at the time of enrollment a bottle of study medication containing 36 doses will be prepared. While children remain in house, the pharmacy will draw study medication into an amber colored syringe from the bottle. At the time of discharge, patients will be discharged with the bottle of remaining study medication and 2 amber colored syringes to draw up the medication at home.

Surgical technique: All patients will be administered 15mg/kg (max dose 650mg) of acetaminophen preoperatively prior to arrival in the preoperative area. General anesthesia will be administered, left to the discretion of each anesthesiologist. After induction, prior to surgical commencement, the patients will receive corticosteroids, either IV dexamethasone 0.5mg/kg (maximum dose of 8mg) or IV methylprednisolone (Solu-Medrol) 2.5mg/kg (max dose 40mg), which is the standard of care at MEEI. The administration of intraoperative steroids not only reduces postoperative edema, but has also been shown to decrease postoperative nausea and vomiting.

The standard method of tonsillectomy among participating surgeons will be extracapsular monopolar electrocautery with standard settings of 12 watts (fulgurate) using a spatula tip. Bleeding will be controlled with suction cautery on a setting of 12-18 watts (fulgurate). Adenoidectomy will be performed at 30 watts (fulgurate). Anesthetic technique, perioperative analgesia with narcotics, and post-operative care will remain equivalent between the two study arms. Antibiotics will not be administered in the perioperative period. Postoperative anti-emetic therapy will be standardized by all collaborating physicians using standardized order sets.

Postoperative period:

No Postoperative Antibiotic Prophylaxis:

Postoperative antibiotics will not be administered based upon the American Academy of Otolaryngology's strong recommendation that antibiotics no longer be used for postoperative prophylaxis after adenotonsillectomy (15). For the first 8 postoperative days (9 days total, POD0-9), children will be administered around the clock, weight based analgesia from medication provided by the inpatient pharmacy at each site.

Postoperative Anti-Emetic Plan:

The following plan for anti-emetics will be used for symptomatic children while hospitalized prior to discharge. No anti-emetics will be administered on an outpatient bases: Ondansetron 0.1mg/kg (max dose 4mg) IV Q8 hours prn nausea/vomiting and/or promethazine 0.25mg/kg IV Q6 hours prn nausea/vomiting.

Postoperative Analgesia:

The pharmacy of each institution will dispense grape-flavored ibuprofen 100mg/5mL (Leader→) or grape-flavored acetaminophen 160mg/5mL (Leader→) based upon the arm to which each participant has been randomized. Ibuprofen will be dosed at 10mg/kg (max dose 600mg) and acetaminophen at 15mg/kg (max dose 650mg), dosing for each will be QID (roughly Q6 hours, however we left dosing QID to allow for some flexibility in the dosing schedule to accommodate patient sleeping schedules). The pharmacy will manipulate the volume of each medication using Ora Blend suspension so that for each child, weight based dosing of each medication will be equivalent in volume. Volume manipulation tables are provided in Appendix A. For each child, an amber colored bottle of 36 doses of study medication will be prepared. The bottle will indicate the patient's name, medical record number, and the volume to be given for each dose of medication. The first dose of study medication will be dispensed 4 hours after the preoperative acetaminophen dose. Thereafter, medication will be dosed QID (or roughly 6 hours apart). Surgeons, nursing staff, and patients and their families will be blinded regarding the type of medication administered (acetaminophen vs. ibuprofen).

At Portsmouth, San Diego and MEEI Sites: nursing staff will draw up study medication in study supplied amber colored syringes from the bottle of study medication. Upon discharge, the patients will be discharged with remaining medication in the bottle, as well as 2 amber colored syringes to draw up medication at home.

At Madigan: Due to nursing regulations, nurses at this institution are not authorized to draw up study medication. At this institution, at the time of enrollment a bottle of study medication containing 36 doses will be prepared. While children remain in house, the pharmacy will draw study medication into an amber colored syringe from the bottle. At the time of discharge, patients will be discharged with the bottle of remaining study medication and 2 amber colored syringes to draw up the medication at home.

Acetaminophen will be given as 15mg/kg dosing (maximum dose 650mg) and ibuprofen will be given as 10mg/kg dosing (maximum dose 600mg). Children with breakthrough pain eligible for narcotics (based upon age, OSA status) will receive weight based doses of oxycodone 1mg/1mL elixir (0.05-0.1mg/kg) as well as be prescribed oxycodone to use for breakthrough pain as an outpatient. After 9 days, patients will be instructed to take acetaminophen 15mg/kg (max dose 650mg) every 4-6 hours as needed for breakthrough pain. They will be instructed not to use nonsteroidal anti-inflammatory drugs (NSAIDS) in the postoperative period (14 days).

Weight based ibuprofen dosing of 10mg/kg was chosen because it is the maximum dose of this medication. Previous studies evaluating ibuprofen use after tonsillectomy used ibuprofen at 5mg/kg (11,12). If ibuprofen is to be used for post-tonsillectomy analgesia, it would likely be used at the maximum dose, similar to the maximum dose of Acetaminophen (15mg/kg) already used in standard practice at our institution. Therefore, we argue that before this practice is instituted, both the analgesic effect as well as the risk of postoperative hemorrhage associated with this dosing need to be further characterized.

The decision to recommend around the clock dosing of analgesics for 9 days was chosen based upon previous studies which indicate that postoperative pain after extracapsular tonsillectomy using electrocautery persists above 2 on the faces pain scale-revised (range 0-6) through POD7 (19). Additionally, studies of postoperative bleeding indicate that the highest risk of incidence of postoperative bleeding occurs on postoperative day 8 (20). Therefore, in order to assess the rate of bleeding associated with ibuprofen use, it seems reasonable to administer the drug throughout the period associated with greatest risk.

A postoperative recommendation form will be placed on each chart for review by the nurses in the recovery room and on the floor (if inpatient status). This form will state that no additional acetaminophen be administered to the participant, and instructing that analgesia be administered from study supplied medication or supplemental narcotics if indicated for breakthrough pain at the discretion of participating surgeons. It will also have standard anti-emetic medications listed.

Pain control data will be collected using a standardized, validated questionnaires as well as additional questions regarding postoperative pain control and return to normal diet and sleep patterns (see attachment at end of proposal). These questionnaires have been used in previous studies evaluating ibuprofen and post-tonsillectomy pain (11, 12). Questionnaires for each postoperative day, as well as a 9 day supply of medication, will be dispensed at discharge. Patient's caregivers will be asked to complete the questionnaire on a daily basis for the day of surgery and first eight postoperative days, and bring it, as well as any remaining study medication, to the postoperative visit for review. Remaining syringes will be assessed to determine the total number of doses of medication each patient received over the 9 day postoperative period.

All participating children and their parents will be advised to see medical evaluation emergently should a bleeding event occur, as is currently standard practice after adenotonsillectomy. All children with evidence of a bleed, such as a history of bleeding, active bleeding, or an oropharyngeal clot will be admitted, at least, for observation, at the discretion of participating surgeons. A large bore IV will be placed and IV fluids administered. Children with active bleeding or a large oropharyngeal clot will return to the operating room, at the discretion of the participating clinician, for control of hemorrhage under general anesthesia and endotracheal intubation. They will be instructed to discontinue the study drug, and take acetaminophen 15mg/kg (maximum dose 650mg) every 4-6 hours for pain control. Children prescribed oxycodone for pain control postoperatively will be able to continue narcotics as well.

At the end of the 14 day postoperative period, a study physician or participating research nurse will conduct a postoperative bleeding questionnaire during the postoperative visit. If a postoperative visit is not planned, investigators will contact patients' parents/guardians to question about postoperative bleeding events. In cases where bleeding occurred, the written and electronic hospital events will be evaluated for further information. Bleeding events will be classified according to the type of intervention taken.

Results will be recorded in an Excel spreadsheet, the latest design of which was approved during the MEEI IRB approval on 5.1.12.

3.2 Allocation to Treatment

Study subjects will be assigned to either the ibuprofen or acetaminophen arm based on a randomization scheme generated by the MEEI pharmacy and distributed to all participating site pharmacies. When a child is enrolled at each site, the pharmacy will assign the child a study number attached to a randomized number (1 or 2), which dictates to which arm the child will be assigned. See below, under "Randomization Procedures" for further details.

3.2.1 Randomization Procedures

Patients will be randomized upon enrollment after obtaining informed consent, and assent when indicated. Randomization will be performed centrally by the Massachusetts Eye and Ear Infirmary pharmacy, and groups of randomization schemes will be distributed to the

pharmacies of participating institutions. The MEEI pharmacy randomization scheme will occur via a one-to-one scheme generated based on a uniform (1, 2) random number generator using "Research Randomizer," which is available online at www.randomizer.org. 722 random number assignments were generated based on an anticipated n = 722. So far, MEEI has been assigned numbers 1-400, San Diego is assigned 401-500, and Madigan is assigned numbers 601-700. *Initially Madigan had received numbers 501-600, however prior to enrollment there was a breach in blinding of this scheme, so the study numbers were thrown out and additional numbers were dispensed to the site.*

3.2.2 Masking Procedures

The surgeon, nurses, and patient/parent will be blinded regarding to which arm the patient has been randomized. Only the pharmacy will know the group to which each study participant has been assigned. The surgeon, nurses, and patients/parents will be blinded regarding to which arm the patient has been randomized. The volume of acetaminophen will be manipulated by each participating pharmacy using OraBlend solution so that the weight-based dose of ibuprofen and acetaminophen are equivalent in volume. The schedule for mixing medication is provided in Appendix A.

3.2.3 Breaking the Mask

If a study patient receives ibuprofen or acetaminophen while taking the study medication, either because of a parental decision or medication error, the study medication will be discontinued. The participating institution's pharmacy will be contacted and the study unblinded for the study subject in question. If concern for overdosing of acetaminophen, liver function tests will be performed, and if concern for overdosing of ibuprofen, kidney function will be testing using BUN and Creatinine.

If a bleeding event occurs, subjects should discontinue the study medication. This will be emphasized verbally at the time of consent and discharge. Additionally, study-specific postoperative instruction sheets will be distributed that also remind parents to discontinue the study medication should a bleeding event occur. After discontinuing the study medication, parents should start acetaminophen 15mg/kg (max dose 650mg) every 4-6 hours as needed for pain. If children are prescribed oxycodone 1mg/kg for breakthrough pain, they may continue this medication.

Patients with bleeding enrolled in the study will be managed in the same fashion as children who are not enrolled, therefore unblinding will not be necessary in the case of each bleeding event.

4. SUBJECT SELECTION

4.1 Subject Inclusion Criteria

- Patients ages 2-18 undergoing tonsillectomy with or without adenoidectomy by electrocautery alone for sleep disordered breathing or infectious tonsillitis.
- Patients with complex medical conditions and craniofacial abnormalities will be included.
- Family must understand and be able to read English.
- Only patients who are not pregnant will be included.
- Informed consent and, when appropriate, child assent will be required for enrollment.

4.2 Subject Exclusion Criteria

- Patients with a known personal or family history of a bleeding disorder will be excluded.
- Patients with a history of asthma, kidney or liver problems will also be excluded.
- Patients with tonsillectomy or adenoidectomy performed using a cold knife technique, microdebrider, coblation or plasma knife.
- Patients on NSAIDs for other medical conditions or those who have taken NSAIDs within 1 week of surgery will be excluded.
- Patients with allergy to aspirin or other NSAIDs, acetaminophen, Red Dye #40 or Red Dye #33 will also be excluded.
- Pregnancy testing using urine beta-HCG will be performed on all children > 13 years of age, or those younger than 13 who are menstruating; this is the testing protocol used at the Children's Hospital of Boston. Patients found to be pregnant will be excluded from participation.
- Patients unwilling to enroll in the study will have the tonsillectomy with or without adenoidectomy performed according to current practice standards.

5. STUDY DRUG(S)/DEVICE(S)

5.1 Study Drug/Device Information

The pharmacy of each institution will dispense grape-flavored ibuprofen 100mg/5mL (Leader→) or grape-flavored acetaminophen 160mg/5mL (Leader→) based upon the arm to which each participant has been randomized. Ibuprofen will be dosed at 10mg/kg (max dose 600mg) and acetaminophen at 15mg/kg (max dose 650mg), dosing for each will be po QID (4 times daily). The pharmacy will manipulate the volume of acetaminophen using Ora Blend suspension so that for each child, weight based dosing of acetaminophen and ibuprofen will be equivalent in volume. See Appendix A for Acetaminophen/OraBlend and Ibuprofen mixing schedules. The first dose will be given 4 hours after the preoperative dose of acetaminophen (15mg/kg, max dose 650mg), then QID (roughly Q6 hours) thereafter for a total of 9 days (the day of surgery and then the first 8 postoperative days, for a total of 36 doses).

5.2 Study Drug/Device Compliance/Adherence

Study subjects will be given instructions about dosing at the time of consent, discharge from the hospital, and in writing on the postoperative instruction sheet. They will be instructed to record administration of each dose of study medication on a dosing sheet, which is provided at the top of each day's postoperative medication and pain questionnaire sheet. At the postoperative visit, the dosing and pain questionnaire sheet will be returned for review. Additionally, any remaining study medication will be collected. The remaining volume of medication will be measured and compared to the volume of each weight-based dose for the study subject. This will allow us to calculate the number of doses actually given.

At the postoperative visit, a study questionnaire will be administered during which patients and their families are asked about whether the study medication was self-discontinued, and whether acetaminophen or ibuprofen were administered during the study period. This information will be recorded.

As we plan to analyze the data using an intention to treat analysis, study subjects that are withdrawn from the study will not be replaced.

5.3 Study Drug Supplies

- **Formulation and Packaging**

The pharmacy of each institution will dispense grape-flavored ibuprofen 100mg/5mL (Leader→) or grape-flavored acetaminophen 160mg/5mL (Leader→) based upon the arm to which each

participant has been randomized. Ibuprofen will be dosed at 10mg/kg (max dose 600mg) and acetaminophen at 15mg/kg (max dose 650mg), dosing for each will be po QID (4 times daily). The pharmacy will manipulate the volume of acetaminophen using Ora Blend suspension so that for each child, weight based dosing of acetaminophen and ibuprofen will be equivalent in volume. See Appendix A for Acetaminophen/OraBlend and Ibuprofen mixing schedules. An expiration date 9 days after study enrollment will be specified to further emphasize that the study medication should not be given after the 8th postoperative day.

At the time of enrollment, 36 weight based doses, calculated to the nearest kilogram, of study medication will be prepared and dispensed in amber colored bottles. Each bottle will be identified by the patient's name, medical record number and instructions regarding the volume of medication to be dispensed for each dose. The pharmacy will also dispense two amber colored syringes from which the medication can be drawn up from the study bottle and volume of each dose measured.

- **Preparing and Dispensing**

The pharmacy at each participating institution will prepare 36 weight based doses of the study medication (dosages specified above). To allow for adequate blinding, OraBlend suspension will be added to acetaminophen so that the weight based volume is equivalent to the weight based volume of ibuprofen. The mixing scheme is provided in Appendix A. Medication will be dispensed in an amber colored bottle with 2 amber colored syringes for drawing up and measuring the volume of each dose of medication. The first dose of study medication will be dispensed 4 hours after the preoperative dose of acetaminophen. Thereafter, study medication will be dispensed QID (four times daily, roughly Q6 hours)

<u>At Portsmouth, San Diego and MEEI Sites</u>: Nursing staff will draw up study medication in study supplied amber colored syringes from the bottle of study medication. Upon discharge, the patients will be discharged with remaining medication in the bottle, as well as 2 amber colored syringes to draw up medication at home.

<u>At Madigan</u>: Due to nursing regulations, nurses at this institution are not authorized to draw up study medication. At this institution, at the time of enrollment a bottle of study medication containing 36 doses will be prepared. While children remain in house, the pharmacy will draw study medication into an amber colored syringe from the bottle. At the time of discharge, patients will be discharged with the bottle of remaining study medication and 2 amber colored syringes to draw up the medication at home.

- **Administration**

The first dose of study medication will be dispensed 4 hours after the preoperative dose of acetaminophen. Thereafter, study medication will be dispensed QID (four times daily, roughly Q6 hours)

At Portsmouth, San Diego and MEEI Sites: Nursing staff will draw up study medication in study supplied amber colored syringes from the bottle of study medication. Upon discharge, the patients will be discharged with remaining medication in the bottle, as well as 2 amber colored syringes to draw up medication at home.

At Madigan: Due to nursing regulations, nurses at this institution are not authorized to draw up study medication. At this institution, at the time of enrollment a bottle of study medication containing 36 doses will be prepared. While children remain in house, the pharmacy will draw study medication into an amber colored syringe from the bottle. At the time of discharge, patients will be discharged with the bottle of remaining study medication and 2 amber colored syringes to draw up the medication at home.

5.4 Study Drug/Device Storage and Accountability

- During hospitalization, the study medication at Portsmouth, San Diego, and MEEI will be kept in Pyxis medication storage systems and accessed when the study medication administration is due.
- During hospitalization at Madigan, the study medication will remain in the inpatient pharmacy so that each dose of study medication can be drawn up and dispensed when administration is due (at this site the nursing staff is not authorized to draw the dose up from a larger volume of medication).
- At home, patients will store the study medication at room temperature. Any remaining medication should be returned at the postoperative visit. At that time the volume of remaining medication will be measured, and the medication will be discarded. The study medication label will indicate an expiration date 9 days after patient enrollment. If study medication is not returned, patients are instructed to discard the medication.

5.5 Other Medications

- **Administration:**

  All study subjects will receive 15mg/kg (max dose 650mg) of acetaminophen orally in the preoperative area. After induction, they should receive IV dexamethasone 0.5mg/kg (maximum dose of 8mg) or IV methylprednisolone (Solu-Medrol) 2.5mg/kg (max dose 40mg). If the patient is eligible to receive postoperative narcotics for breakthrough pain, they may be prescribed oxycodone 1mg/1mL elixir (0.05-0.1mg/kg) in addition to the study medication. They should not receive antibiotic prophylaxis at the time of surgery or during the postoperative period. They may receive Ondansetron 0.1mg/kg (max dose 4mg) IV Q8 hours prn nausea/vomiting and/or promethazine 0.25mg/kg IV Q6 hours prn nausea/vomiting while hospitalized. No antiemetics should be administered at home.

- **Rescue Medication or Therapy**

  If study subjects do not have adequate pain control on the study medication and oxycodone elixir, when eligible to receive this medication, they may be removed from the study and given another narcotic for postoperative pain. Any children removed from the study for this reason will be recorded.

6. BIOSPECIMEN COLLECTION (IF APPLICABLE)

Biospecimen collection is not applicable for this study.

7. STUDY PROCEDURES

7.1 Screening Procedures

Subjects will be identified when they are scheduled for a tonsillectomy and approached to participate in this study. Their electronic medical record will be reviewed to confirm they meet inclusion criteria and do not meet exclusion criteria. If they meet all inclusion criteria and none of the exclusion criteria, subjects will be asked to participate in the study.

7.2 Enrollment/Baseline Procedures

The study will be introduced to the patients and his or her family at time the tonsillectomy is scheduled. The Principal Investigator of each participating site will introduce the study and answer any questions patients and their families may have. On the day of surgery, investigators will reapproach patients and their families about enrollent. They will be given the opportunity to consider participation prior to arrival in the preoperative area. Only those who sign an informed consent form before surgery will be included in the study.

Written, informed consent will be obtained from the parent or guardian of each participating child under the age of 18. Children 18 years of age will sign their own informed consent. Only personnel approved by each participating center's IRB will obtain consent. Personnel will be available to answer any questions that participants and their families may have.

Consent may be obtained at the preoperative visit or on the day of surgery preoperatively. If consent is obtained during the preoperative visit, procedures will be reviewed with the child and their parent on the day of surgery to confirm their willingness to participate.

Obtaining written assent will be considered for all children over the page of 12. As each child's degree of maturity will vary, whether or not to obtain written assent will be left to the discretion of personnel obtaining consent. In the assent form, children will be notified that a urine sample for pregnancy testing will be requested for all female participants > 13 years of age and/or are menstruating.

A colored piece of paper identifying the patient's study participation and postoperative guidelines will be placed on the front of each participant's chart. This will be used to guide nurses and responding clinicians in their management of participating patients.

Date of Surgery

1. **Pre-Anesthesia Unit:** All subjects should receive a preoperative dose of acetaminophen 15mg/kg (max dose 650mg) by mouth in the preoperative waiting area prior to surgery.

2. **Intraoperative Anesthesia:** Subjects will undergo endotracheal intubation and general anesthesia. The type of anesthesic agents administered to each child will be left to the discretion of participating anesthesiologists. No standard anesthesia plan will be used as children's needs may be vary intraoperatively. However, children will be administered intraoperative steroids and will not receive intraoperative or postoperative antibiotics.

    a. **Steroid administration.** The administration of intraoperative steroids not only reduces postoperative edema, but has also been shown to decrease postoperative nausea and vomiting. After induction, all children should be administered dexamethasone (Decadron) 0.5mg/kg (max dose 8mg) IV OR methylprednisolone (Solu-Medrol) 2.5mg/kg (max dose 40mg) IV.

    b. **No antibiotics will be administered intraoperatively or in the postoperative period.** This is based upon recently published post-tonsillectomy guidelines published by the American Academy of Otolaryngology.

3. **Surgical Technique**
    a. Tonsillectomy: The standard method of tonsillectomy among participating surgeons will be extracapsular monopolar electrocautery with the standard settings of 12 watts fulgurate using a spatula tip.
    b. Hemostasis: Bleeding will be controlled with a suction cautery on a setting of 12-18 watts fulgurate.
    c. Adenoidectomy: The standard method of adenoidectomy with suction cautery will be performed at 30 watts fulgurate.

4. **Post-Anesthesia Care:** Children will receive standard postoperative care in the recovery room; the agents used will be left to the discretion of participating anesthesiologists. In this setting, children may receive antiemetics and additional narcotics if needed. However, acetaminophen will not be administered postoperatively. Four hours after the preoperative dose of acetaminophen, children may start receiving the study drug.

5. **Postoperative Anti-emetic Plan:** The following plan for anti-emetics will be used for symptomatic children while hospitalized prior to discharge. No anti-emetics will be administered on an outpatient bases: Ondansetron 0.1mg/kg (max dose 4mg) IV Q8 hours prn nausea/vomiting and/or promethazine 0.25mg/kg IV Q6 hours prn nausea/vomiting.

7.3 Study Drug or Device Procedures

a. The pharmacy of each institution will dispense grape-flavored ibuprofen 100mg/5mL (Leader→) or grape-flavored acetaminophen 160mg/5mL (Leader→) based upon the arm to which each participant has been randomized. Ibuprofen will be dosed at

10mg/kg (max dose 600mg) and acetaminophen at 15mg/kg (max dose 650mg). 36 doses of the study medication will be prepared and dispensed in an amber colored bottle with two amber colored syringes. The first dose will be given 4 hours after the preoperative acetaminophen dose. Thereafter, the study medication will be given QID.

b. Whether or not a child is also eligible to receive narcotic medication for breakthrough pain will be left to the discretion of each participating care-giver.
    i. If narcotics are to be given, children should receive oxycodone 1mg/1mL elixir at 0.05-0.1mg/kg dosing every 4-6 hours.
    ii. Oxycodone may be given while the child is an inpatient, as well as prescribed for home use.
    iii. If narcotics are given, children should also continue to receive the study drug four times daily (QID).
c. Subjects should continue the study medication four times daily (QID) on the day of surgery, as well as the first 8 postoperative days (9 days total). They should continue until study medication supplies have been exhausted, unless study medication remains after postoperative day 8. After this time, the study patient should receive acetaminophen 15mg/kg (max dose 50mg) every 4-6 hours as needed for pain. If the child was prescribed oxycodone elixir postoperatively they may continue this medication as well.
d. Parents' family members will be asked to fill out study medication dosing and pain control questionnaires each day, starting on postoperative day 0, the day of surgery, even if the child remains a patient on the in-patient ward, through postoperative day 8.
e. Study subjects and their parents should be asked to save any unused study medication, and to bring the bottle to their postoperative visit for collection along with medication dosing and pain questionnaires.

Pain control Data Acquisition

1. Patients and their family members will receive a packet of 9 study medication dosing and pain control questionnaires along with the study drug, and will be instructed to fill out this questionnaire at the end of each postoperative day (9 days total, postoperative day 0-8). See Appendix B.
2. Study subjects and their parents will be asked to bring these questionnaires to their first postoperative visit for collection.
3. Study subjects will also be asked to the bottle of any remaining study medication. This will allow study personnel to assess compliance with study guidelines, and to determine each child's medication exposure.

Bleed Data Acquisition

1. All subjects should be instructed to go to the emergency room if there is any evidence of postoperative bleeding for evaluation and treatment.

2. As is currently standard practice at MEEI, all children with a history of bleeding, or those with active bleeding or evidence of an oropharyngeal clot, will be admitted, at least, for observation. However, this will be left to the discretion of the treating emergency room physician. If the child is admitted, a large bore IV will be placed and fluids administered.
3. Children with active bleeding or a large oropharyngeal clot will return to the OR, at the discretion of the covering clinician, for control of hemorrhage under general anesthesia with endotracheal intubation. Again, however, this will be left to the discretion of the treating phyisician.
4. If bleeding occurs within the first 8 postoperative days, chidren will be advised to discontinue the study drug, and to take tylenol 15mg/kg (maximum dose 650mg) Q4-6 hours as needed for pain. Those children prescribed oxycodone postoperatively may continue to use it as well if needed.
5. At the end of the 14 day postoperative period, or at the time of the postoperative visit, a study physician or participating research nurse will conduct a postoperative bleeding questionnaire and ask each study participants' parents or guardian questions about any postoperative bleeding events.
6. In cases where bleeding is reported, written and electronic hospital records will be evaluated for further information so that bleeding events can be classified according to the type of intervention taken.
    a. Bleeding events will be classified according to the following:
        i. Primary vs. Secondary
            1. Primary: bleed occurs < 24 hours after surgery
            2. Secondary: bleed occurs >/= 24 hours after surgery
        ii. Levels 1-3
            1. Level 1: children with any history of postoperative bleeding, regardless of whether there was clinical evidence of bleeding upon medical evaluation. This level includes all children with a history of postoperative bleeding who presented for evaluation/treatment by a physician in the Emergency Department, inpatient unit or operating room.
            2. Level 2: children who required inpatient admission for postoperative hemorrhage regardless of the need for operative intervention. This level of severity excludes children who were evaluated in the emergency room who had no clinical evidence of hemorrhage or clot and were deemed safe for discharge home without admission for observation or intervention.
            3. Level 3: the highest level of severity, includes children who required hospital admission and return to the operating room for control of post-tonsillectomy hemorrhage.
        iii. The location where the surgery took place, as well as the participating surgeon should be noted for each bleeding event.
    b. The DSMB must be notified of each bleeding event that is discovered in study subjects, as well as the total enrollment for the site at that time.

i. After enrollment of 100 subjects at MEEI, if the objective, type 3 bleed rate exceeds 6% (three times the expected average of 2% based on review of the literature and MEEI quality and outcomes data), the study will be put on hold until further evaluation has been performed. The study will be terminated if the type 3 bleed rate in either arm exceeds 9.3%.
ii. On a bi-annual basis (every 6 months) after 100 patients have been enrolled, the data from all participating institutions will be pooled and reviewed. If the type 3 bleed rates exceed 6% in either study arm, the study will be terminated.
iii. An interim analysis will be performed at enrollment of 102 patients. If type 3 bleeding in the ibuprofen group is 3% above the acetaminophen group, with $p<0.000001$, or if the type 3 bleed rate exceeds 6% (> 7 bleeds), the study will be terminated.
iv. Another interim analysis will be performed at the half-way point, after enrollment of the 362nd subject. If type 3 bleeding in the ibuprofen group is 3% above the aceteminophen group, with $p< 0.001525$, the study will be terminated. The study will also be terminated if bleeds occur in > 22 patients (type 3 bleed rate > 6%).

G. Data Analysis

1. At the completion of enrollment, 722 participants, the study will be terminated and data reviewed using both univariate and multivariate analysis.
    a. A simple, uni-variate analysis will be performed to evaluate the association between ibuprofen and bleeding (we are primarily interested in evaluating the association between ibuprofen and type 3 bleeding).
        i. The null hypothesis (ibuprofen does not increase the risk of type 3 postoperative hemorrhage) will be rejected if there is a greater than 3% increase, which is the preset equivalence margin, in type 3 bleeding in the ibuprofen cohort in comparison to the acetaminophen cohort with a p value of 0.025.
    b. A multi-variate logistic regression model will be used to evaluate ibuprofen exposure, pain control, outcome and potential confounding factors such as narcotics use, age, surgical indication, gender, and operating surgeon.

7.4 Standard of Care Procedures

- Pregnancy testing using urine beta-HCG assays will be performed on all female participants over the age of 13, or those less than 13 years of age who are menstruating. Subjects will not be randomized into treatment groups until the results of this testing are obtained. All subjects found to be pregnant will be excluded from the study.
- All patients will be administered 15mg/kg (max dose 650mg) of acetaminophen preoperatively prior to arrival in the preoperative area and dexamethasone 0.5mg/kg IV (maximum dose of

8mg) or methylprednisolone (SoluMedrol) 2.5mg/kg IV (maximum dose of 40mg) in the operating room prior to surgical commencement, which is standard practice at MEEI.

- The standard method of tonsillectomy among participating surgeons will be extracapsular monopolar electrocautery with standard settings of 12 watts (fulgurate) using a spatula tip. Bleeding will be controlled with suction cautery on a setting of 12-18 watts (fulgurate).
- Adenoidectomy will be performed at 30 watts (fulgurate).
- Anesthetic technique, perioperative analgesia with narcotics, and post-operative care will remain equivalent between the two study arms.
- Antibiotics will not be administered in the perioperative period.
- Postoperative anti-emetic therapy will be standardized by all collaborating physicians using standardized order sets.
- All patients will be prescribed postoperative analgesia, and those eligible to receive narcotics will also be prescribed oxycodone elixir. Postoperative hemorrhage will be managed the same, regardless of study participation.

7.5 Follow-up Procedures (Incorporate only if follow-up procedures will be performed)

After the 14 day study period, a postoperative questionnaire will be administered to ask about bleeding events and use of acetaminphen or ibuprofen during the study period. Postoperative study medication dosing and pain questionnaires will be collected. Any remaining study medication will be collected and the volume of remaining medication recorded.

7.6 Unscheduled Visits

At the end of the 14 day study period, the patient's chart will be reviewed. Any unscheduled visits, Emergency Room visits or phone calls will be noted. If the child had a bleeding event, whenever available, hospital records will be reviewed to document the extent of bleeding and intervention taken.

7.7 Early Termination

Patients who are removed from the study due to noncompliance, intolerance of the study medication, or any other reason will be recorded.

7.8 Schedule of Activities (Study Table)

8. SAFETY AND EFFECTIVENESS ASSESSMENTS

8.1 Safety Assessments

- Not applicable. Ibuprofen at 10mg/kg and Acetaminophen 15mg/kg are drugs commonly used in children ages 2-18 and have been shown to be effective analgesics after tonsillectomy. Urine beta-HCG testing will be performed per MEEI protocol to ensure female participants are not pregnant prior to study drug administration.
- Should a patient inadvertently receive ibuprofen or acetaminophen in addition to the study drug during the study period, they will undergo liver function test or BUN, creatinine testing to monitor liver and kidney function.

8.2 Effectiveness Assessments

- At the end of the 14 day postoperative period, study questionnaires will be collected and a postoperative bleeding questionnaire conducted.

9. ADVERSE EVENT RECORDING AND REPORTING

Definition: Please refer to the HSC's Policy on "Reporting Adverse Events and Unanticipated Problems" for definitions used by the Human Studies Committee. If your definitions of adverse events is different, please define here.

9.1 Recording Requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) or device(s) will be recorded in the subjects' case histories (source data, case report form). For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s) or device(s).

Adverse events or abnormal test findings felt to be associated with the study drug(s) or device(s) will be followed until the event (or its sequel) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

➢ **ABNORMAL TEST FINDINGS**

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
- Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the Sponsor-Investigator of the IND or IDE application

➢ **CASUALTY AND SEVERITY ASSESMENT**

The Sponsor-Investigator of the IND or IDE application will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the Sponsor-Investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s)", the adverse event will be classified as associated with the use of the study drug(s) for reporting purposes. If the Sponsor-Investigator's final determination of causality is "unknown but not related to the study drug(s)", this determination and the rationale for the determination will be documented in the respective subject's case history (source data or case report form).

9.2 REPORTING PROCEDURES

- **REPORTING OF ADVERSE EVENTS TO FDA**
  - The drugs used in this study are FDA approved, and this study is not part of an FDA trial.
- **Reporting Adverse Events to Other External Entities**
  - Adverse Events will be reported to the IRB of the participating institution, as well as investigators at other study sites.
- **Reporting Adverse Events to the Human Studies Committee (Please follow HSC Policy "REPORTING ADVERSE EVENTS AND UNANTICIPATED PROBLEMS")**

9.3 Withdrawal of Subjects due to Adverse Events

- Study subjects are instructed to discontinue the study drug and switch to acetaminophen 15mg/kg (max dose 650mg) by mouth every 4-6 hours as needed for pain should a bleeding event occur. The patient may continue oxycodone elixir if they were prescribed this medication for breakthrough pain postoperatively.
  - Should a bleeding event occur, it will be classified as primary or secondary, and by severity (type 1, type 2, or type 3). Guidelines for these classifications are outlined in section 7.3 of this document.
  - Patients who experience a bleeding event will still come to their follow-up appointment, which is scheduled at the time their surgery was booked.
- Study subjects will be withdrawn from the study if they receive acetaminophen or ibuprofen during the study period, if they self-discontinue the study medication, or if the medication was stopped and they were started on a different medication for postoperative analgesia.
- Subjects removed from the study will remain in the analysis using an intention to treat model.

10. STATISTICAL METHODS/DATA ANALYIS

10.1 Primary endpoint(s) or outcome measure(s)

1. **Pain control Data Acquisition**
   - Patients and their family members will receive a packet of 9 study medication dosing pain control questionnaires (see Appendix B) along with the study drug, and will be instructed to fill out this questionnaire at the end of each postoperative day (9 days total, postoperative day 0-8). See Appendix B.
   - Study subjects and their parents will be asked to bring these questionnaires to their first postoperative visit for collection.
   - Study subjects will also be asked to bring the bottle of any remaining study medication. This will allow study personnel to assess compliance with study guidelines, and to determine each child's medication exposure.
2. **Bleed Data Acquisition**
   1. All subjects should be instructed to go to the emergency room if there is any evidence of postoperative bleeding for evaluation and treatment.
   2. As is currently standard practice at MEEI, all children with a history of bleeding, or those with active bleeding or evidence of an oropharyngeal clot, will be admitted, at least, for observation. However, this will be left to the discretion of the treating emergency room physician. If the child is admitted, a large bore IV will be placed and fluids administered.
   3. Children with active bleeding or a large oropharyngeal clot will return to the OR, at the discretion of the covering clinician, for control of hemorrhage under general anesthesia with endotracheal intubation. Again, however, this will be left to the discretion of the treating phyisician.
   4. If bleeding occurs within the first 8 postoperative days, chidren will be advised to discontinue the study drug, and to take tylenol 15mg/kg (maximum dose 650mg) Q4-6 hours as needed for pain. Those children prescribed oxycodone postoperatively may continue to use it as well if needed.
   5. At the end of the 14 day postoperative period, or at the time of the postoperative visit, a study physician or participating research nurse will conduct a postoperative bleeding questionnaire and ask each study participants' parents or guardian questions about any postoperative bleeding events.
   6. In cases where bleeding is reported, written and electronic hospital records will be evaluated for further information so that bleeding events can be classified according to the type of intervention taken.
      a. Bleeding events will be classified according to the following:
         i. Primary vs. Secondary
            1. Primary: bleed occurs < 24 hours after surgery
            2. Secondary: bleed occurs >/= 24 hours after surgery

ii. Levels 1-3
    1. Level 1: children with any history of postoperative bleeding, regardless of whether there was clinical evidence of bleeding upon medical evaluation. This level includes all children with a history of postoperative bleeding who presented for evaluation/treatment by a physician in the Emergency Department, inpatient unit or operating room.
    2. Level 2: children who required inpatient admission for postoperative hemorrhage regardless of the need for operative intervention. This level of severity excludes children who were evaluated in the emergency room who had no clinical evidence of hemorrhage or clot and were deemed safe for discharge home without admission for observation or intervention.
    3. Level 3: the highest level of severity, includes children who required hospital admission and return to the operating room for control of post-tonsillectomy hemorrhage.
iii. The location where the surgery took place, as well as the participating surgeon should be noted for each bleeding event.

10.2 Secondary endpoints or outcome measure(s)

- We will look at bleeding and pain data and its relationship to the age and gender of the study subject, participating institutuion, surgeon, and indication for surgery.

10.3 Sample Size Determination

In order to determine our sample size, we looked at data collected at our institution (MEEI) during a previous study investigating post-tonsillectomy bleeding when steroids were given intraoperatively (Dr. Gallagher and Dr. Hartnick's study of the use of dexamethasone and the risk of postoperative bleeding, in press awaiting JAMA publication). In this cohort, 137 children received dexamethasone and postoperative acetaminophen, and there were 3 type 3 bleeds requiring return to the operating room for control of hemorrhage, giving a roughly 2% type 3 bleed rate. This is consistent with MEEI quality and outcomes data for 2005-2009, which demonstrated that 2.25% (SD 0.5) of tonsillectomies performed during this period required return to the operating room (type 3 bleeding) for control of hemorrhage. Therefore, we used a type 3 bleed rate of 2% as our predicted type 3 bleed rate for patients in the control, acetaminophen arm.

From literature review of prospective trials, meta-analyses and retrospective reviews, the average NSAID bleed rate is 10.9%, representing roughly a 6% increase in bleed rate. Previous studies designed to evaluate bleeding rates as a primary outcome measure were powered to only detect a significance between treatment groups if bleed rates differed by >20%. Based on consensus judgment among the PI, AI and key personnel with review of the literature, it was agreed that the potential benefits conferred by ibuprofen would be acceptable provided the

administration was associated with no more than a 3% absolute increase in bleeds requiring operative intervention compared to the standard treatment of acetaminophen.

Dr. Rie Maurer then calculated a projected sample size using a group sequential two proportions non-inferiority method using East v 5.4.2 and O'Brien-Flemming stopping boundaries determined by means of the Lan-DeMets approach with the following parameters: an alpha of 0.025, power of 80%, 5% projected lost to follow-up rate, acetaminophen (control) type 3 bleed rate of 2%, noninferiority diference of 3%, and 3 anticipated unblinded looks at the data. Using these parameters, the following sample sizes were calculated:

One sided alpha	Power	Proportion of bleeding in Acetaminophen group	Non inferiority Difference	Sample size
0.025	80%	2%	3%	343 per group, 686 total (361 per group,722 total with loss of Fu 5%)

Look	Accumulated info	Accumulated Sample Size	Z value boundary	Cum. Alpha spent
1	14%	48 per group; 96 total (51 per group 102 total with loss of Fu 5%)	5.877	<0.000001
2	50%	172 per group; 344 total (181 per group; 362 total with loss of Fu 5%)	2.963	0.001525
3 (final)	100%	343 per group; 686 total (361 per group; 722 total with loss of Fu 5%)	1.969	0.025

10.4 Analysis Population (if applicable)

- We plan to use an intention to treat method when we unblind and analyze our data.

10.5 Effectiveness Analysis (if applicable)

We plan to initially analyze the crude association between ibuprofen and bleeding rate using simple, univariate analysis. We will then construct a multivariate logistic regression model including ibuprofen exposure, pain control, outcome, and potential confounding factors such as age, surgical indication, gender, and operating surgeon. Analysis will be performed using an intention to treat analysis. Impact of losses to follow-up will be assessed using sensitivity analysis. Statistical analysis and data management will be performed using STATA, SAS and Microsoft Excel.

Interval looks at the data are planned. If, after enrollment of 100 children at MEEI, then on a bi-annual basis, if the type 3 bleed rate does not exceed 9.3%, the study will continue recruitment until n= 102. At that time, a first look of the data will be planned. If the bleed rate in the ibuprofen exceeds 3% that in the acetaminophen group with a $p<0.000001$, recruitment will be terminated. If not, as long as type 3 bleed rate remains < 6%, recruitment will continue until n=362. At that time, a second unblinded look at the data is planned. If the noninferiority margin exceeds 3% with a $p<0.001525$, the study will be terminated. If not and the type 3 bleed rate remains < 6%, the study will continue until we reach a total n= 722. If the ibuprofen group bleeding rate exceeds 3% with a $p<0.025$ at that time, ibuprofen will be considered inferior to the control, acetaminophen group.

Please note that this statistical plan deviates from the original plan outlined in the MEEI protocol approved on 5.2.12. When an acetaminophen control group type 3 bleed rate became available, we felt it was important to use this in our sample size calculations. In previous literature reviews. Type 3 bleed rates were not available, and previous control group bleed rates were based on all types of bleeding. Additionally, because we planned to perform a look at the bleed rate after enrollment of 100 participants as part of our initial safety analysis, we felt it would be appropriate to perform an unblinded look at the data at that time, for patient safety, and to account for this in our sample size calculations.

10.6 Safety Analysis

Interval looks at the data are planned. If, after enrollment of 100 children at MEEI, then on a bi-annual basis, if the objective, type 3 bleed rate does not exceed 9.3%, the study will continue recruitment until n= 102. At that time, a first look of the data will be planned. If the bleed rate in the ibuprofen exceeds 3% that in the acetaminophen group with a $p<0.000001$, recruitment will be terminated. If not, as long as the type 3 bleed rate remains < 6%, recruitment will continue until n=362. At that time, a second unblinded look at the data is planned. If the noninferiority margin exceeds 3% with a $p<0.001525$, the study will be terminated. If not and the type 3 bleed rate remains < 6%, the study will continue until we reach a total n= 722. If the ibuprofen group bleeding rate exceeds 3% with a $p<0.025$ at that time, ibuprofen will be considered inferior to the control, acetaminophen group.

10.7 Interim Analysis

Interval looks at the data are planned. If, after enrollment of 100 children at MEEI, then on a bi-annual basis, if the type 3 bleed rate does not exceed 9.3%, the study will continue recruitment unless otherwise instructed after DSMB review. We will plan to perform a first look at the data at n= 102. If the bleed rate in the ibuprofen exceeds 3% that in the acetaminophen group with a $p<0.000001$, recruitment will be terminated. If not, as long as type 3 bleed rate remains < 6%, recruitment will continue with permission of our DSMB until n=362. At that time, a second unblinded look at the data is planned. If the noninferiority margin exceeds 3% with a $p<0.001525$, the study will be terminated. If not and the type 3 bleed rate remains < 6%, the study will continue with permission of the DSMB until we reach a total n= 722. If the ibuprofen group bleeding rate exceeds 3% with a $p<0.025$ at that time, ibuprofen will be considered inferior to the control, acetaminophen group.

10.8 Data and Safety Monitoring

- The DSMB at MEEI is comprised for Dr. Stacey Gray, Dr. Maynard Hansen, and Dr. Mark Volk.
- Each time a bleeding event occurs, the institution's DSMB and investigators at all participating institutions will be notified with a summary of the event (primary or secondary bleed, type of bleeding (type 1, 2 or 3) and circumstances surrounding the bleed. The DSMB will be notified regarding the total enrollment and overall bleed rate at that time.
    - If type 3 bleeding rates exceed 6% after enrollment of at least 100 subjects at MEEI (three times the expected rate of 2% based on review of the literature and MEEI quality and outcomes data), the study will be put on hold at all sites pending further investigation. If the type 3 bleed rate exceeds 6% in either study arm, the study will be terminated
    - On a bi-annual basis (every 6 months) after at least 100 patients have been enrolled, the data from all participating institutions will be pooled and reviewed. If type 3 bleed rates exceed 6%, the study will be unblinded. If type 3 bleeding exceeds > 6% in either study arm, the study will be terminated.
    - The DSMB will evaluate data from each of the 3 looks of the data. During the first two looks, the DSMB will determine if the study should continue.

12. DATA HANDLING AND RECORD-KEEPING

12.1 Data Recording and Record-Keeping

Each subject will have an entry in an electronic spreadsheet, maintained in a password Microsoft Excel Document available only to investigators with the study. Source data describes the clinical findings, observations, and other information contained in the patient's electronic and hospital records, pharmacy dispensing records. Pertinent source data for each subject will be entered into their entry on the spreadsheet.

The electronic data recording data system being used for this clinical research study has not been fully certified as being compliant with the FDA regulations at 21 CFR Part 11 due to the limited scope of this clinical research study.

14. STUDY DISCONTINUATION CRITERIA

14.1 Discontinuation of Individual Research Subjects

- See conditions under Section 5.2

14.2 Sponsor-Investigator Discontinuation of the Clinical Research Study

- There is no study related sponsor.

15. APPENDICES

15.1 Schedule of Events

Activity	Screening	Date of surgery (Postoperative day 0)	Postoperative days 1-8	Postoperative day 9	Bleeding Event	End of 14-day postoperative period/follow-up visit
Informed consent	X	X				
Inclusion/Exclusion Criteria	X					
Urine beta-HCG testing for female patients who meet screening criteria (standard preop practice at MEEI)	X	X				
Randomization		X				
Pharmacy prepares and dispenses bottle with 36 doses of study medication		X				
Dosing and pain questionnaires distributed		X				
Postoperative instructions distributed		X				
Dosing and pain questionnaires filled out		X	X			
Stop Study Medication				X	X	
Start acetaminophen 15mg/kg po Q4-6 hours prn pain				X	X	
Physician exam/evaluation					X	X
Collect remaining study medication						X
Collected completed dosing and pain questionnaires						X
Administer bleeding questionnaire						X
Monitor for adverse events		X	X	X	X	X
Monitor compliance					X	X

15.2 Case Report Form(s)

Case report forms are not being used for this study. The latest version of our excel spreadsheet for recording data was approved by the MEEI IRB on 5/1/1.