RESEARCH PROTOCOL

Effectiveness of a Combined Acetaminophen and Ibuprofen Regimen for Management of Post-Tonsillectomy Pain in Pediatric Patients

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Study Title	**Effectiveness of Combined Acetaminophen and Ibuprofen Regimen for Management of Post-Tonsillectomy Pain in Pediatric Patients**	
Objectives	To compare the effectiveness of a combined regimen of acetaminophen and ibuprofen dosed every 6 hours with the current practice of alternating acetaminophen and ibuprofen every 3 hours in the treatment of post-operative tonsillectomy pain in the pediatric population.	
Study Period	1 year	
Number of Subjects	200 subjects' ages 4-17 who undergo tonsillectomy with or without adenoidectomy at St. Louis Children's Hospital (SCLH) and the Children's Specialty Care Center (CSCC).	
Study Treatment	A combined acetaminophen and ibuprofen medication regimen administered every 6 hours following surgery through the end of post-operative day (POD) 3 compared against the current practice of alternating acetaminophen and ibuprofen every 3 hours following surgery through the end of post-operative day 3.	
Study Design	Single-center, randomized, open-label, non-inferiority treatment pilot study to evaluate the effectiveness of a combined acetaminophen and ibuprofen regimen for treatment of post-operative tonsillectomy pain in the pediatric population. 200 children undergoing tonsillectomy will be randomized to receive either a combined acetaminophen and ibuprofen regimen dosed every 6 hours or an alternating regimen of acetaminophen and ibuprofen dosed every 3 hours.	
Inclusion and Exclusion Criteria	<u>Inclusion Criteria</u> a) 4 to 17 years of age at time of enrollment b) Undergoing tonsillectomy with or without adenoidectomy c) Able to provide informed consent from parent or legal guardian d) Able to provide assent if subject is a minor of appropriate age	<u>Exclusion Criteria</u> a) Allergy to acetaminophen or ibuprofen b) Inability for study participant to cooperate with pain assessments c) Known pregnancy d) Any condition which would make the participant, in the opinion of the investigator, unsuitable for the study
Measurements	Pain scores will be measured in the post-anesthesia care unit (PACU) when first awakening, at 30 minutes, and then hourly after PACU arrival, as well as at the time of discharge and prior to administration of rescue medication. Safety assessments will be performed as standard of care in the PACU. A medication log will be given to subjects to assess their adherence to the study regimen, duration of medication usage, and use of break through analgesic medication. Follow up surveys to assess pain scores will be sent to participants twice a day on post-operative day (POD) 1, 3, and 7. Pain will be assessed using the standardized FLACC scale for all subjects, as well as an additional assessment using the standardized Wong-Baker Faces scale for subjects ages 7 and older.	
Outcomes	**<u>Primary</u>**: The proportion of FLACC pain scores ≥7 from POD 1 through POD 3 between the combined and the alternating medication regimens **<u>Secondary</u>**: (between the combined and the alternating medication regimens) 1. The proportion of FLACC pain scores ≥7 on each individual POD 1, 3, and 7 2. The proportion of cumulative FLACC pain scores ≥7 from POD 1 through POD 7 3. The proportion of Faces pain scores ≥8 on POD 1, 3, and 7 4. The proportion of cumulative Faces pain scores ≥8 from POD 1 through POD 7 5. The proportion of rescue medication usage from POD 1 through POD 3 6. The proportion of rescue medication usage from POD 1 through POD 7 7. Adherence to the assigned study medication regimen 8. Incidence of adverse events	

1. Background and Rationale:

Tonsillectomy is the 2nd most common outpatient pediatric surgical procedure performed in the U.S. with over half a million surgeries annually. The two main primary indications for pediatric tonsillectomy are recurrent infections and sleep disordered breathing (SDB)[1]. Tonsillectomy is defined as a surgical procedure performed with or without adenoidectomy that completely removes the tonsil, including its capsule, by dissecting the peritonsillar space between the tonsil capsule and muscular wall[1]. They are relatively low risk surgical procedures usually done as a same-day surgery[2]. The Royal College of Surgeons of England found that tonsillectomies had a delayed discharge rate of 1.9 % due to various reasons, including post-op pain, hemorrhage, respiratory complications, and vomiting. The top reason for these delays was inadequate pain control accounting for 36% of delayed discharges [3]. Acute pain can cause stress, fear, and anxiety for both the patient and the caregiver [4]. Furthermore, it is also associated with poor oral intake, vomiting, and sleep disturbances for the patient [5]. Thus, adequate post-op pain control is an essential component to ensuring timely healing and patient well-being following surgery. Additionally, according to prior research done on adult tonsillectomy patients, the incidence of severe pain, defined as pain ≥7 on a 10-point scale, is 14.5% on post-op Day 1, 39.9% on Day 3, 28.4% on Day 7 [6].

One of the most widely used drugs for post-operative pain relief in tonsillectomy prior to 2013 was codeine. Codeine is a prodrug that is metabolized to morphine via the CYP2D6 enzyme, providing an oral form of pain control that was thought to have a good safety profile [7]. However, recent research has found significant genetic variability in this enzyme, where poor metabolizers get little or no pain relief while ultra-rapid metabolizers are at high risk for respiratory depression [8]. Although genetic testing for CYP2D6 exists, it is expensive, and normal metabolizers may still experience adverse effects. In 2013, the FDA issued a “black box warning” for codeine, advising health care professionals “to prescribe an alternative analgesic for postoperative pain control in children” [8]. Furthermore, a randomized trial in SDB patients undergoing tonsillectomy found that the number of desaturation events per hour (preoperative to postoperative) was reduced by a mean of 1.79 ± 7.57 in the group given ibuprofen compared with an average increase of 11.17 ± 15.02 in the morphine group [9]. Thus, identifying the best alternatives to opioids for post op pain control for pediatric tonsillectomy patients are critical.

The main alternatives are acetaminophen and NSAIDs. Scheduled acetaminophen is the recommended first line treatment for post op pain relief following discharge from the hospital [10]. However, to ensure adequate pain control, acetaminophen is generally used in conjunction with other drugs, namely opioids [1] However, a potential alternative to opioids are NSAIDs. NSAIDs were initially avoided due to the potential increased risk of bleeding and hemorrhage when compared to opioids [11]. However, this conflicts with a recent Cochrane review of 900 patients from various RCTs that demonstrated no increased risk of bleeding with NSAIDs use in post-tonsillectomy patients compared to patient that did not receive NSAIDs [12]. Thus, the current guidelines from the American Academy of Otolaryngology-Head and Neck surgery recommend the use of NSAIDs alongside acetaminophen for post-tonsillectomy pain relief[1]. A recent trial in adults compared a combined acetaminophen+ ibuprofen regimen against only acetaminophen or only ibuprofen and found that the combined regimen had improved pain control [13]. This suggests that a combined regimen may be superior to a single non-opioid analgesic strategy. Furthermore, there is also evidence of potential synergistic effects when the 2 drugs are given at the same time [14]. Some otolaryngologists at SLCH currently advise their patients to take acetaminophen and ibuprofen on an alternating basis, with one drug administered every 3 hours, but each drug only given every 6 hours. This is done on the belief that more frequent analgesic dosing will provide superior pain control. However, this practice has never been compared directly to giving both drugs simultaneous every 6 hours.

Necessary caretaker involvement in the pediatric population adds a new layer of complexity to medication dosing. Adhering to various, often confusing or tedious, pain control

regimens post-operatively can be a challenge for caregivers who are balancing many other aspects of life while caring for the child. This is especially true for families with caregivers who are working and cannot always be available around the clock to give frequent scheduled pain medication. Furthermore, despite various oral formulations, children do not enjoy taking medications, which can further frustrate caretakers. The American Academy of Family Physicians notes these limitations and suggests having a simplified regimen to assist patients and families in adhering to the medication regiment [15]. Thus, we aim to assess a means to limit this confusion while also assessing pain control and patient satisfaction. We will compare a combined regimen where both acetaminophen and ibuprofen are administered together every 6 hours, with a regimen that is currently practiced at St. Louis Children's Hospital where acetaminophen and ibuprofen are alternated, one medication given every three hours. There is currently a dearth of information regarding adherence to medication regimens and we hope our study will help elucidate a more convenient regimen with equal or improved pain control to a more tedious current standard pain control regimen [16].

In this study, we will compare the common post-tonsillectomy pediatric pain regimen of alternating acetaminophen and ibuprofen every three hours with a regimen in which a patient is given both medications every 6 hours. Since the black box warning placed on codeine, there has been no one standard of care, for post-tonsillectomy pain. We hope that this study will provide objective data regarding optimal pain control for this patient population.

2. Objectives

The goal of this research proposal is to assess the effectiveness of two dosing regimens in controlling post-tonsillectomy pain in pediatric populations. We aim to assess how a combined scheduled dosing regimen of acetaminophen and ibuprofen every 6 hours compares with the dosing regimen currently used at SLCH of alternating acetaminophen and ibuprofen every 3 hours. We hope to show that a combined regimen is non-inferior in terms of instances of severe pain experienced by patients following hospital discharge, and/or in need for rescue pain medication to the alternating regimen.

In addition, we believe that based on the current guidelines for pediatric post-tonsillectomy pain control, the simultaneous administration of acetaminophen and ibuprofen may play a significant role in improving patient satisfaction and compliance. This regimen was relatively well tolerated with minimal adverse events reported in adults undergoing dental surgery [13]. A recent double-blind study performed in adults following wisdom teeth removal showed improved pain control with a combined regimen when compared to either acetaminophen or ibuprofen alone[13]. However, there is a dearth of studies to guide therapy in the pediatric population. We hope to expand on this by introducing a new regimen that may be easier to follow, and will likely improve compliance and satisfaction amongst patients and caregivers. Furthermore, there are no studies comparing a combined dose of acetaminophen and ibuprofen administered at the same time versus an alternating dosing strategy. As the combined dosing strategy is markedly easier for families to comply with, if it is non-inferior to the alternating dosing strategy, it would likely be preferred.

This pilot study is the first step in determining both the safety and effectiveness of combined pain medication vs. the current practice of alternating each medication regimen following tonsillectomy in pediatric populations. It will allow us to assess the degree of difference in both pain relief and patient satisfaction while also assessing for any unforeseen adverse outcomes. We will use information gleaned here to power and design a larger scale study.

3. Preliminary Data

Over the past year from 2017-2018, there were over 700 tonsillectomies and adenotonsillectomies performed at St. Louis Children's Hospital (SLCH) and the ambulatory surgery center at the Children's Specialty Care Center (CSCC). The ages of the patients ranged from 1 to 18 and indications included recurrent infections, sleep disordered breathing, and a variety of other conditions. These numbers illustrate the feasibility of conducting a study of 100 patients in a reasonable time frame, ideally in less than 1 year.

4. Patient Selection

Subjects will be recruited through the St. Louis Children's Hospital (SLCH) Otolaryngology Department. Subjects will be approached prior to surgery in person. Prior to study initiation written informed consent will be obtained from subjects' parent or legal guardian, and assent will be obtained from minors of appropriate age. Goal enrollment is 200 children (4-17 years old) who are undergoing tonsillectomy with or without adenoidectomy.

4.1. *Inclusion Criteria*

- 4.1.1. 4 to 17 years of age at time of enrollment
- 4.1.2. Undergoing tonsillectomy with or without adenoidectomy
- 4.1.3. Able to provide informed consent from parent or legal guardian
- 4.1.4. Able to provide assent if subject is a minor of appropriate age

4.2. *Exclusion Criteria*

- 4.2.1. Allergy to acetaminophen or ibuprofen
- 4.2.2. Inability for study participant to cooperate with pain assessments
- 4.2.3. Known pregnancy
- 4.2.4. Any condition which would make the participant, in the opinion of the investigator, unsuitable for the study

5. Methods:

5.1. Study design:

Single-center, randomized, open-label, non-inferiority pilot study.

5.2 Enrollment

The surgery schedule at SLCH is posted in advance which allows us to evaluate daily for eligible subjects to approach for inclusion. The patients' medical record will be screened for: age of child, type of surgical procedure planned, pertinent medical history, whether the child is in the custody of a legal caregiver, and ability to consent/assent to the study. Eligible candidates scheduled to undergo tonsillectomy at SLCH will be approached either in the outpatient setting or preoperative holding area prior to surgery by a member of the study team. Study details will be explained and informed consent obtained from parents or legal guardian, and assent as appropriate.

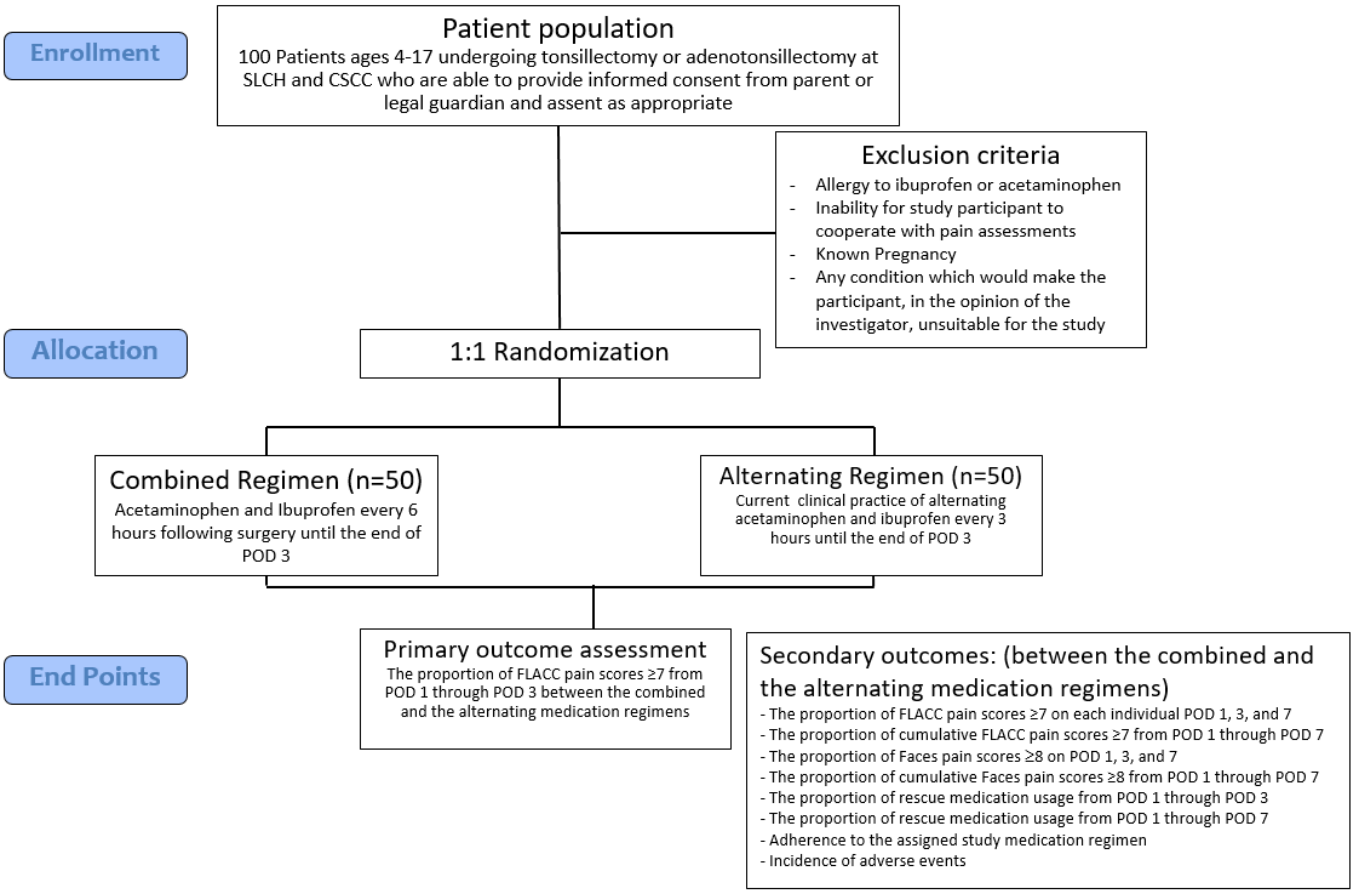

Figure 1. Study Protocol

5.3 Treatment phase

Patients will be randomized to one of two post-operative pain control medication regimens through POD 3. Randomization will follow a block randomization with blocks of 10 subjects. To maintain allocation concealment the research associate who assigns patients has no knowledge of the randomization sequence. The study clinicians will not be blinded, as they will be required to write prescriptions and caregivers will not be blinded as they will carry out the assigned treatment regimen. Participants will be randomized to either the alternating medication regimen, which is the current practice of alternating doses of acetaminophen and ibuprofen every 3 hours following surgery through the end of POD 3 or the combined medication regimen, which is a combined administration of acetaminophen and ibuprofen every 6 hours following surgery through the end of POD 3.

As standard of care, all patients will receive a single dose of intravenous acetaminophen intraoperatively which will also serve as time-point 0. The combined treatment group will receive the first dose of oral (PO) ibuprofen in the post-anesthesia care unit (PACU) with all subsequent doses given as a combination of PO acetaminophen and ibuprofen every 6 hours (with IV acetaminophen counting as time-point 0). The alternating treatment group will receive the first dose of PO ibuprofen 3 hours after the intra-operative IV acetaminophen. All subsequent doses of alternating PO acetaminophen and ibuprofen will be given on an alternating basis, every 3 hours.

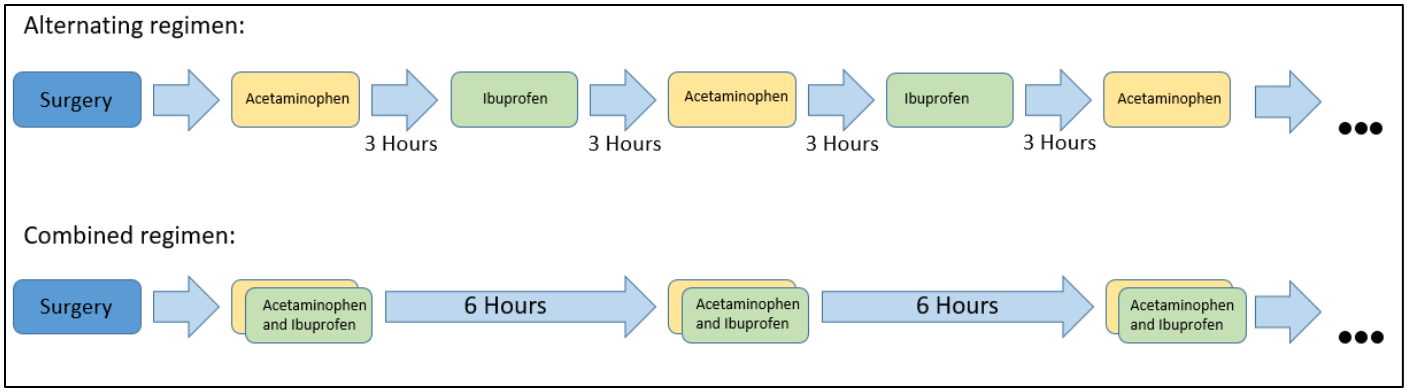

Figure 2. Pain medication regimens for each arm of the study.

Post operatively pain scores will be measured in the PACU when first awakening, at 30 minutes, and then hourly after PACU arrival, as well as at the time of discharge and prior to administration of rescue medication. Safety assessments will be performed as standard of care in the PACU. Follow up surveys to assess pain scores will be sent to participants twice a day on POD 1, 3, and 7. In the event a participant doesn't have an email address or access to a smartphone or computer, they will be sent home with a copy of the surveys and the study team will call them to obtain the responses. Pain will be assessed using the standardized FLACC scale for all subjects, as well as an additional assessment using the standardized Wong-Baker Faces scale for subjects ages 7 and older. Note that the day of surgery is post-operative day 0. Pain assessment surveys will be sent electronically to participants via Redcap or completed through the MyCap app on their smartphone. Participants will be given the option to utilize MyCap to receive their follow up surveys. Mycap is a mobile phone application that allows research participants to report outcomes directly to a REDCap database using their personal mobile phone or tablet. A traditional REDCap database is utilized to setup the data collection instruments and store study data. MyCap translates the defined REDCap instruments into a format compatible with Android or IOS devices and allows participants to complete them from their mobile device. Once a task is completed, MyCap converts the results into a format compatible with REDCap before synchronizing back to the REDCap database. Perceived likeability of the assigned medication regimen will be assessed on POD 3 using a 7 point Likert scale.

Orders and prescriptions for medication will be provided by the operating surgeons. Patients who are admitted post operatively will have their medication regimen administered by hospital nursing staff until their discharge. The timing of these medications and any breakthrough analgesic medications will be obtained from the patient's electronic medical record. Upon discharge, the timing of acetaminophen and ibuprofen, and the use of any break through analgesic medication will be recorded by caregivers in a paper journal provided by the study team. Upon completion of the study regimen, at the end of POD 3, caregivers may continue to provide analgesic medications as needed using whichever regimen they prefer. We will continue to collect medication usage, and pain scores through POD 7 regardless of medication timing after POD 3.

All patients will be prescribed a rescue analgesic medication, oxycodone, for breakthrough pain relief as needed. Caregivers will be provided with a copy of the FLACC criteria, and Wong-Baker Faces scoring criteria if the subject is 7 years of age or older, as well as instructions on how to properly score on the 2 different scales.

FLACC scale (Face, Legs, Cry, Activity Consolability scale)	Score
Face 0- No particular expression or smile 1- Occasional grimace or frown, withdrawn, disinterested 2- Frequent to constant frown, quivering chin, clenched jaw	
Legs 0- Normal position or relaxed 1- Uneasy, restless, tense 2- Kicking or legs drawn up	
Activity 0- Lying quietly, normal position, moves easily 1- Squirming, shifting back and forth, tense 2- Arched, rigid, or jerking	
Cry 0- No cry (awake or asleep) 1- Moans or whimpers; occasional complaint 2- Crying steadily, screams or sobs, frequent complaints	
Consolability 0- Content, relaxed 1- Reassured by occasional touching, hugging, or being talked to; distractile 2- Difficult to console or comfort	
Total score (0-10)	

Figure 3. FLACC scale
https://www.researchgate.net/publication/283575369_Physicians'_use_of_pain_scale_and_treatment_procedures_among_children_and_youth_in_emergency_primary_care_-_a_cross_sectional_study

Figure 4. Wong-Baker Faces scale via the Wong-Baker Faces Foundation
https://wongbakerfaces.org/

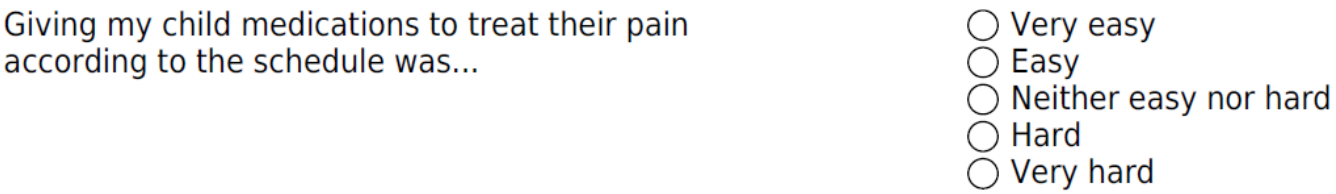

Figure 5. Likert Scale

5.4. Conclusion of study

The study period for each subject ends once all surveys are submitted. The total time spent per subject for this study will be approximately 8 days.

6. Data Collection and Monitoring

6.1. Demographic Data

After consent is obtained we will collect basic demographic information (age, race, gender), indication for tonsillectomy, surgical technique, and pertinent medical history.

6.2. Clinical Assessments

Prior to pain medication administration the patient will undergo a focused history and physical exam performed by a member of the research team to check contraindications to the proposed medications.

6.3 Pain Assessments

Post operatively pain scores and safety assessments will be measured in the PACU upon awakening, prior to administration of any rescue medications, and prior to discharge. Following discharge from the hospital, each study participant's caregiver will receive online surveys to complete twice a day (12 hours apart) on POD 1, 3, and 7. Caregivers will be requested to complete one survey between 6am and 9am and another survey between 6pm and 9pm. Surveys will be distributed via Redcap. They will evaluate and record the following information prior to the administration of the morning and evening medications that day:

1) Patient's Faces, Legs, Arms, Cry, Consolability (FLACC) score for all children (Fig. 3)
2) Patient's Wong-Baker Faces Pain Scale score for children ages 7 and older (Fig. 4)
3) Dose in milligrams of rescue pain medication (oxycodone) used in the past 12 hours
4) Has the patient experienced severe pain >= 7/10 on either scale. (yes or no)
5) Any adverse events since the surgery or submission of the previous survey
6) Ease of use of the assigned regimen on the Likert scale rated from very easy to very difficult

6.4 Medication Log

Time and date of medication administration will be obtained from the subjects' electronic medical record during their time in the PACU and for those admitted post operatively. Upon discharge a paper medication log will be given to subjects to record the time and date medication is administered. This log will be used to assess adherence to the study regimen, duration of medication usage, and use of break through medication.

7. Outcome Measures

7.1 Primary Outcome

The cumulative proportion of FLACC pain scores ≥7 from POD 1 through POD 3 between the combined and the alternating medication regimens

7.2. Secondary Outcome Measures (between the combined and the alternating medication regimens)

7.2.1. The proportion of FLACC pain scores ≥7 on each individual POD 1, 3, and 7
7.2.2. The proportion of cumulative FLACC pain scores ≥7 from POD 1 through POD 7
7.2.3. The proportion of Faces pain scores ≥8 on POD 1, 3, and 7
7.2.4. The proportion of cumulative Faces pain scores ≥8 from POD 1 through POD 7
7.2.5. The proportion of rescue medication usage from POD 1 through POD 3
7.2.6. The proportion of rescue medication usage from POD 1 through POD 7
7.2.7. Adherence to the assigned study medication

7.2.8. All adverse events including but not limited to presenting to the emergency department for severe bleeding, anorexia, or intractable nausea or vomiting.

7.3 Exploratory Outcome Measures

7.3.1. Comparison of pain scores in patients over versus under the age of 12

Perception of pain and the expression of pain vary considerably amongst older and younger patients. The FLACC scale in particular, has components such as crying and body movements that may not entirely reflect the expression of pain in older children in particular. Thus in order to account for this difference, we would like to conduct a separate analysis for children above and below the age of 12 to ensure there are no significant differences between the groups, If there are significant differences, we will report those in a stratified analysis.

7.3.2. Comparison of pain scores based on surgical technique

Surgical technique for tonsillectomy can be divided into 3 major categories: cold dissection, electrocautery, and harmonic scalpel tonsillectomy. The cold knife method removes the tonsils by use of a standard scalpel and is the most common procedure. The electrocautery method burns tonsillar tissue and assists with bleeding, but causes thermal injury to surrounding tissue. Studies show that although bleeding was significantly lower, pain intensity at 4 and 24 hours post-surgery was significantly higher[17]. Finally, the Harmonic scalpel uses ultrasonic energy to vibrate the blade, which results in simultaneous cutting and couterizing[18]. Previous studies have shown that the use of the Harmonic scalpel during surgery reduces both the volume of intra-operative bleeding and pain intensity level on postoperative day one[19]. Thus given these findings, surgical technique is a potential confounder in the study which we will account for by doing a stratified subgroup analysis to detect any strata specific differences.

7.4. Analysis

This is a non-inferiority pilot study comparing the proportion of patients with severe pain (FLACC score≥7) in the combined regimen vs. the alternating regimen. Our null hypothesis is that the combined regimen is inferior to the currently used alternating regimen and our alternative hypothesis is that it is non-inferior. Based on clinical judgment, the margin within which we will consider the proposed combined dosing regimen to be similar in effectiveness to the current clinical practice of an alternating regimen is 0.15. Based on prior studies in adult tonsillectomy patients using a 10-point scale, the incidence of severe pain (≥7) on post-op Day 1 is 0.145, Day 3 is 0.399, and Day 7 is 0.284, with a final total proportion of pain ≥7 divided by total pain scores collected of 0.194[6]. There is no data analyzing these proportions with our proposed combined regimen as it is a novel medication regimen not used before.

Pain between POD 1 and POD 3 was chosen as the primary outcome because prior research has indicated POD 3 to be the day with most severe pain in adults[6]. In order to obtain this proportion, we will first convert FLACC pain scores (graded on a 10 point scale) into a binary outcome: those with severe pain (scores ≥7) and those without severe pain (scores ≤ 7). We chose 7 as pain scores ≥7 are considered to be “severe” based on prior studies[6,17]. In addition to providing current pain assessments, caregivers will also be asked whether or not their child had severe pain since they left the hospital (first survey) or since they last filled out a previous survey (all other surveys).

As this is a pilot study, we based our sample size on 2018-2019 hospital data which revealed that over 700 pediatric tonsillectomies +/- adenoidectomies were conducted at the St. Louis Children’s Hospital and Children’s Specialty Care Center combined. Thus we plan to approach and recruit at least 100 patients for our study. The secondary outcome measures are the proportion of patients with severe pain (FLACC score ≥7), the average use of breakthrough pain medication, and all adverse events. Thus, if the hypothesis is correct, we anticipate no significant difference with using the alternating versus combined pain regimen in pediatric patients

undergoing tonsillectomy. We hope that these findings will allow for a more simplified pain regimen with ease of use amongst caregivers.

8. Potential Risks

8.1. Breach of confidentiality

There is minimal risk associated with the collection and recording of patient medical record numbers to permit review of the patient's medical record.

MyCap App Security:

Participant data is stored locally on the device in an AES-256+SHA2 encrypted database. Data remains on the device if an internet connection is not available. Applies to both iOS and Android devices.

When an internet connection is available, data is transmitted to REDCap using an SSL connection. A hash-based message authentication code (HMAC) is used to verify the integrity of the data and to authenticate the sender.

Data is deleted from the device after the MyCap app verifies that data has been successfully transmitted.

Authentication to Device:

Participants create a 6-digit PIN that is used to open the MyCap, this is in addition to the authentication already on their device.

8.2. Combined acetaminophen and ibuprofen risk

There is minimal risk associated with either acetaminophen or ibuprofen. The American Academy of Otolaryngology-Head and Neck Surgery Foundation makes a strong recommendation that "clinicians should recommend ibuprofen, acetaminophen, or both for pain control after tonsillectomy."[1]

8.3 Steps Taken to Mitigate Risk

Studies are conducted under the supervision of the investigating physicians who are trained and experienced in performing research in human subjects, and in monitoring local anesthetic related adverse effects.

Inclusion and exclusion criteria, monitoring, and the clinical protocol are designed to ensure that risks are minimal. Subjects are informed that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty. A pregnancy test will be performed on women of childbearing potential, as is standard of care, and subjects excluded if pregnant. Subjects will be told that in the event of a physical injury as the direct result of study procedures, they will be cared for by a member of the investigating team at no cost, within the limits of the Washington University compensation plan.

The first dose of both regimens will be administered while the patient is in the post-operative recovery area with monitoring for any adverse effects. If the patient is unable to tolerate the treatment they may request to be removed from the study or may be removed by the principle investigator if they are unable to complete the study.

Regarding confidentiality; 1) all subjects will be assigned a study ID number, 2) The link to identifiers will be destroyed at the end of the study. 3) Data will be stored under lock and key (office, file cabinet) and only the investigators and research team will have access. If data are published, there will be no link to identifiers. Study data will not be revealed to any organization, individuals other than the subjects, or the subjects themselves. 4) Study data will not be entered in subjects' medical records.

9. Management of Intercurrent Events

9.1. Adverse Experiences

The investigator will closely monitor subjects for evidence of adverse events. All adverse events will be reported and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, intensity, etiology, relationship to the study drug (none, unlikely, possible, probable, highly probable), and any treatment required.

9.2. Premature Discontinuation

If a subject withdraws from the study, the subject will be replaced to provide the required number of subjects. Subjects will be withdrawn if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study.

10. Data and Safety Monitoring Plan

Studies conducted in the Department of Anesthesiology follow the Washington University Institutional Review Board Policies and Procedures (last revision January 21, 2019). All individuals working on the study are required to read and be familiar with and compliant with the IRB Policies and Procedures. The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to the use of ibuprofen and acetaminophen. Based on the small size and relatively low risk nature of the protocol, the investigating physicians are involved in the monitoring plan. A full DSMB is not needed. These individuals will review the annual summary of adverse events. In addition, they will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event. The investigators will follow the requirements for principle investigator reporting requirements as outlined in Section X of the IRB Policies and Procedures.

References:

1. Mitchell, R. B. *et al.* Clinical Practice Guideline: Tonsillectomy in Children (Update). *Otolaryngol. Neck Surg.* **160**, S1–S42 (2019).
2. Ingram, D. G. & Friedman, N. R. Toward Adenotonsillectomy in Children: A Review for the General Pediatrician. *JAMA Pediatr.* **169**, 1155–1161 (2015).
3. National Prospective Tonsillectomy Audit Final Report. *Royal College of Surgeons* https://www.rcseng.ac.uk/library-and-publications/rcs-publications/docs/tonsillectomy-audit/.
4. Power, N. M. *et al. Correspondence to*. (2012).
5. Stanko, D., Bergesio, R., Davies, K., Hegarty, M. & von Ungern-Sternberg, B. S. Postoperative pain, nausea and vomiting following adeno-tonsillectomy - a long-term follow-up. *Paediatr. Anaesth.* **23**, 690–696 (2013).
6. Álvarez Palacios, I., González-Orús Álvarez-Morujo, R., Alonso Martínez, C., Ayala Mejías, A. & Arenas Brítez, O. Postoperative Pain in Adult Tonsillectomy: Is There Any Difference Between the Technique? *Indian J. Otolaryngol. Head Neck Surg.* **69**, 187–193 (2017).
7. Lauder, G. & Emmott, A. Confronting the challenges of effective pain management in children following tonsillectomy. *Int. J. Pediatr. Otorhinolaryngol.* **78**, 1813–1827 (2014).
8. Tobias, J. D., Green, T. P., Coté, C. J., Medicine, S. on A. and P. & Drugs, C. O. Codeine: Time to Say "No". *Pediatrics* **138**, e20162396 (2016).
9. Kelly, L. E. *et al.* Morphine or Ibuprofen for Post-Tonsillectomy Analgesia: A Randomized Trial. *Pediatrics* **135**, 307–313 (2015).

10. Ismail Zaidan & Amanda Lent. Post-Tonsillectomy Pain in Children: The Postcodeine Era. *US Pharm.* **41**, 31–34 (2016).
11. D'Souza, J. N., Schmidt, R. J., Xie, L., Adelman, J. P. & Nardone, H. C. Postoperative nonsteroidal anti-inflammatory drugs and risk of bleeding in pediatric intracapsular tonsillectomy. *Int. J. Pediatr. Otorhinolaryngol.* **79**, 1472–1476 (2015).
12. Lewis, S. R., Nicholson, A., Cardwell, M. E., Siviter, G. & Smith, A. F. Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database Syst. Rev.* (2013) doi:10.1002/14651858.CD003591.pub3.
13. Merry, A. F. *et al.* Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. *BJA Br. J. Anaesth.* **104**, 80–88 (2010).
14. Miranda, H., Puig, M., Prieto, J. & Pinardi, G. Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. *Pain* **121**, 22–28 (2006).
15. Promoting Medication Adherence in Children - American Family Physician. https://www.aafp.org/afp/2006/0901/p793.html.
16. Brian Haynes, R., Ann McKibbon, K. & Kanani, R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *The Lancet* **348**, 383–386 (1996).
17. Uitti, J. M., Salanterä, S., Laine, M. K., Tähtinen, P. A. & Ruohola, A. Adaptation of pain scales for parent observation: are pain scales and symptoms useful in detecting pain of young children with the suspicion of acute otitis media? *BMC Pediatr.* **18**, (2018).

Washington University in St. Louis

INFORMED CONSENT DOCUMENT

Project Title: Effectiveness of a Combined Acetaminophen and Ibuprofen Regimen for Management of Post-Tonsillectomy Pain in Pediatric Patients

Principal Investigator: David Leonard

Research Team Contact: Dr. David Leonard 314-454-2136

- If you are the parent/guardian of a child under the age of 18 who is being invited to participate in this study, the word "you" in this document refers to your child. As the parent/guardian, you will be asked to read and sign this document to give permission for your child to participate.
- If you are under the age of 18 and reading this document, the word "you" in this document refers to you. You will be asked to read and sign this document to indicate your willingness to participate.

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you are scheduled to undergo a tonsillectomy with or without adenoidectomy at St. Louis Children's Hospital (SCLH) and the Children's Specialty Care Center (CSCC).

The purpose of this research study is to compare the effectiveness of a combined regimen of acetaminophen and ibuprofen dosed every 6 hours with the current practice of alternating acetaminophen and ibuprofen every 3 hours in the treatment of post-operative tonsillectomy pain.

Acetaminophen and ibuprofen are approved by the U.S. Food and Drug Administration to reduce pain and fever.

WHAT WILL HAPPEN DURING THIS STUDY?

You will be randomized (like flipping a coin) to either:

- the alternating medication regimen which is the current practice of alternating doses of

acetaminophen and ibuprofen every 3 hours following surgery through the end of post-operative day 3 (POD 3); or

- the combined medication regimen which is a combined dose of acetaminophen and ibuprofen every 6 hours following surgery through the end of POD 3

Surgery will occur per standard protocol. The surgery itself is not part of the research, however information about the surgery, including medications given during surgery, will be recorded for research purposes. As standard of care, all patients will receive a single dose of intravenous (IV) acetaminophen during surgery.

The alternating treatment group will receive the first dose of oral ibuprofen 3 hours after the intra-operative IV acetaminophen. All subsequent doses of alternating oral acetaminophen and ibuprofen will be given on an alternating basis, every 3 hours. Dosages are done as standard of care.

The combined medication group will receive the first dose of oral ibuprofen in the post-anesthesia care unit (PACU) with all subsequent doses given as a combination of oral acetaminophen and ibuprofen every 6 hours. Dosages are done as standard of care.

All patients are prescribed a rescue pain medication for breakthrough pain relief as needed. Breakthrough pain is severe pain that occurs while a patient is already medicated with a long-acting painkiller.

Post operative pain scores will be measured when first awakening, at 30 minutes, and then hourly after PACU arrival, as well as at the time of discharge and prior to administration of rescue medication (medicine intended to relieve your symptoms immediately) if rescue medication is needed.

Follow up surveys to assess pain scores will be completed twice a day on post-op days 1, 3, and 7.

In the event you don't have an email address or access to a smartphone or computer, you will be sent home with a copy of the surveys and the study team will call you to obtain your responses.

You will record the timing of acetaminophen and ibuprofen, and the use of any breakthrough pain medication in a paper journal provided to you. Upon completion of the study medication regimen, at the end of POD 3, you may continue to provide pain relieving medications as needed using whichever regimen you prefer. You will continue to record medication usage and timing and pain scores through POD 7.

We will collect information about you and your medical history as it relates to the surgery from your medical record for up to 30 days This information will be used for research.

Will you save my <u>research information to use in future research studies?</u>

We would like to use the data we are obtaining in this study for studies going on right now as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding post-tonsilectomy pain management in pediatric patients or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not

yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your data you give up any property rights you may have in the data.

We will share your data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at Washington University, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

If you change your mind and do not want us to store and use your data for future research you should contact the research team member identified at the top of this document. The data will no longer be used for research purposes. However, if some research with your data has already been completed, the information from that research may still be used. Also, if the data has been shared with other researchers it might not be possible to withdraw the data to the extent it has been shared.

Please place your initials in the blank next to Yes or No for each of the questions below:

My data may be stored and used for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

My data may be shared with other researchers and used by these researchers for the future research as described above.

_____ Yes **_____ No**
Initials **Initials**

Identifiers may be removed from your private information and used for future research or shared with others. If this occurs, we will not ask you for additional consent.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 100 people will take part in this study conducted by investigators at Washington University.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for approximately 8 days. We will be collecting data from their medical record for up to 30 days following your surgery.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Ibuprofen

Allergy alert - May cause severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- Hives
- Facial swelling
- Asthma (wheezing)
- Shock
- Skin reddening
- Rash
- Blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning – ibuprofen contains NSAID, which may cause severe stomach bleeding. The chance is higher if you:

- Have had stomach ulcers or bleeding problems
- Take a blood thinning or steroid drug
- Take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen or others)
- Take more or for a longer time than directed

Heart attack and stroke warning – NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Acetaminophen

Liver warning - Severe liver damage may occur if you use more than directed. In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222).

Breach of Confidentiality

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?

You may or may not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because it will allow us to assess safety and effectiveness of combined pain medication versus the current practice of alternating each medication regimen following tonsillectomy.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could receive the same medications without being in the research study.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You and/or your medical/hospital insurance provider will remain responsible for your regular medical care expenses including the pain relieving medications.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

The University and the research team are not receiving payment from other agencies, organizations, or companies to conduct this research study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator Dr. Leonard at 314-454-2136 and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about whether payment for medical treatment for injuries relating to your participation in research will be made by Washington University**.** If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

Other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you. We will keep your participation in this research study confidential to the extent permitted by law.

- Government representatives (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Hospital or University representatives to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and will be available to anyone with access to your health care record, including your health

insurance company. This information may also be released as part of a release of information request.

- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.
- Any report or article that we write will not include information that can directly identify you. The journals that publish these reports or articles require that we share your information that was collected for this study with others to make sure the results of this study are correct and help develop new ideas for research. Your information will be shared in a way that cannot directly identify you.

To help protect your confidentiality, we will assign you a study ID. The master list linking you and your study ID will be kept separate from your research record. Any report or article that we write will not include information that can directly identify you. The journals that publish these reports or articles require that we share your information that was collected for this study with others. Sharing this information will allow others to make sure the results of this study are correct and help develop new ideas for research. Your information will be shared in a way that cannot directly identify you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

Can we contact you by email?

We would like to contact you by email for the purposes listed below. Some of these emails may contain health information that identifies you.

- **Survey completion; appointment scheduling containing PHI**

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above. If you have any questions or need to contact us for an urgent or emergent situation, please contact the research team member identified at the top of this document.

You should be aware that there are risks associated with sending your health information via email.

- There is always a risk that the message could be intercepted or sent to the wrong email address. To avoid sending messages to the wrong email address, the first email we send you will be a test message to ensure we have the correct email address.
- When using any computer you should be careful to protect your username and password. Make sure you log-out before getting up from the computer.
- If you share a home computer with other family members, and do not want them to know you are participating in this study make sure you provide an email address that only you can access.
- Your employer will have access to any email communications sent or received on any electronic devices used for work or through a work server.

Do you agree to allow us to send your health information via email?

_____ **Yes** _____ **No**
Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?

Under certain circumstances, the investigator might decide to end your participation in this research study earlier than planned. This might happen for no reason or because **in our judgment it would not be safe for you to continue.**

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: **Dr. Leonard at 314-454-2136.** If you experience a research-related injury, please contact: **Dr. Leonard at 314-454-2136.**

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 02/09/22.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Parent/Guardian Name and Relationship to Participant:

Do not sign this form if today's date is after EXPIRATION DATE: 02/09/22.

_____
(Child's name – printed)

_____ _____
(Signature of Parent/Guardian) (Date)

_____ _____
(Name of Parent/Guardian- printed) (Relationship to participant – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____

(Signature of Person who Obtained Consent) (Date)

_____

(Name of Person who Obtained Consent - printed)