Study title: Anesthesia with Neuromuscular Blockade and Reversal with Sugammadex Compared to Anesthesia without Muscle Relaxation During Pediatric High-Risk Adenotonsillectomy: A Randomized-Controlled Trial

NCT number: NCT06225466

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Investigator Studies Program (MISP)
Clinical Protocol Template

Requirements for Submitting a Full Clinical Protocol

Section #1 - MISP Protocol Identification

Study Title:	*The title of the protocol should include study design, indication and, where applicable, dosage, dosage form, and comparative agent(s).* *Example:* *A double-blind, randomized, parallel design study to compare the effectiveness of losartan versus hydrochlorothiazide in reversing or preventing the progression of the remodeling of resistance arteries in subjects with pre-hypertension and pre-diabetes* Anesthesia with Neuromuscular Blockade and Reversal with Sugammadex Compared to Anesthesia without Muscle Relaxation During Pediatric High-Risk Adenotonsillectomy: A Randomized-Controlled Trial
Request Date:	**9/1/2023**
Institution Name	**University of Texas Southwestern Medical Center**
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	*2.1 List the objectives.* *The objectives must clearly define and specifically state what the study is intended to accomplish. Most studies have one primary efficacy and one primary safety objective.* *One to two secondary objectives may be stated. They should be in the order of priority. The higher priority secondary objectives should have corresponding secondary hypotheses associated with them. Not all secondary objectives need to have a corresponding secondary hypothesis* **Primary Efficacy Objective** – Evaluate intraoperative and postoperative opioid consumption in high-risk children having adenotonsillectomy (AT) without muscle relaxation or with neuromuscular blocks and reversal with sugammadex. **Secondary Objectives** – (1) Evaluate postoperative respiratory events in high-risk children having AT without muscle relaxation or with neuromuscular blocks and reversal with sugammadex. The outcome of postoperative respiratory events will be a composite measure consisting of 1) airway obstruction or hypoxemia, defined as SpO2 <90%, requiring any of the following interventions: supplemental oxygen by nasal cannula or simple face mask, noninvasive positive airway pressure, or reintubation; or 2) unanticipated ICU admission. (2) Evaluate postoperative low minute ventilation (MV) episodes, defined as MV < 40% predicted for at least 2 minutes and measured by a respiratory volume monitor, in high-risk children having AT without muscle relaxation or with neuromuscular blocks and reversal with sugammadex. *2.1.1 List the clinical hypotheses.* *The primary efficacy and safety hypotheses should correspond directly with the primary objectives of the study. All hypotheses should be in the order of priority. If the study is estimation study, no hypotheses is needed.* AT is one of the most *performed pediatric surgeries*, with over 550,000 procedures performed annually in the US.[1] Postoperative respiratory complications occur in up to 46% of children after AT.[2] Previously identified risk factors include young age, severity of obstructive sleep apnea (OSA), and comorbidities.[3, 4] This risk of harm is not only detrimental for *patient safety*, but also results in substantial *healthcare costs and resource utilization*. Due to this risk of harm, children with identified risk factors are recommended for overnight admission following AT for respiratory monitoring.[5] Previously identified risk factors have all been related to demographic and clinical characteristics that cannot be modified. Modifiable factors, particularly as they relate to anesthetic management during AT, have received little evaluation. It is currently unknown if certain aspects of anesthetic management may decrease the risk of respiratory events after pediatric AT. *There is a critical need to identify anesthetic regimens that decrease the risk of respiratory events after AT.* If unable to meet this need, there will be a block to vertical advancement of the perioperative care of children having AT, with continued high rates of respiratory complications and cost and resource utilization for prolonged postoperative monitoring. AT is a relatively short procedure, typically lasting about 30-45 minutes, with high-intensity stimulation and thus pain level. Neuromuscular blocks reduce anesthetic and analgesic requirements by reducing non-purposeful movement during painful stimulation. With near constant electrocautery during AT, movement with painful stimulation is difficult to treat without neuromuscular blockade. Subsequently,

higher doses of anesthetics and opioid analgesics are required to prevent movement. The effects of these agents take time to dissipate, and as our preliminary data show , being under a deep plane of anesthesia at the time of extubation and opioid exposure increase the risk of respiratory problems (see “Background, Rationale, and Preliminary Data” below). Despite the potential benefits of utilizing neuromuscular blockade during anesthetic management of pediatric AT, it is not standard of care primarily because of outdated concerns that needing to reverse neuromuscular blockade prolongs the time from the end of surgery until extubation. This additional time is not well tolerated because of the inherent production pressure that results from high turnover operating schedules with many short surgeries and the expectation of highly efficient anesthetic management. Classic neuromuscular blockade reversal agents include acetylcholinesterase inhibitors that require some inherent recovery of neuromuscular function prior to administration. This recovery of function takes time, and in some very short cases like AT, the surgery may be finished before any recovery has occurred. The anesthesiologist would then have to wait until the recovery occurs to give an acetylcholinesterase inhibitor for reversal of neuromuscular blockade. Sugammadex is a selective neuromuscular blocking reversal agent that completely and effectively reverses neuromuscular blockade even with a deep block.[6] The development of sugammadex provides a safe and effective reversal of neuromuscular blockade even during short cases, allowing anesthesiologists the benefits of the use of neuromuscular blockade during cases of any duration. Because high doses of inhaled and intravenous anesthetics and opioids are typically required to prevent movement, the primary benefit of using neuromuscular blockade is a decrease in anesthetic and opioid administration. Preliminary data from our group found 2 modifiable risk factors for postoperative respiratory events: a deep plane of anesthetic at the end of surgery and *opioid exposure*. Therefore, we expect neuromuscular blockade administration with sugammadex reversal to reduce respiratory events after AT.

Our long-term goal is to identify causative, modifiable aspects of perioperative management of children having AT that result in postoperative respiratory events. Our overall objective in this application is to determine if the use neuromuscular blockade in the anesthetic management of high-risk children having AT decreases opioid requirements, and therefore the risk of respiratory events*. Our central hypothesis is that anesthetic management using neuromuscular blockade with adequate reversal by sugammadex, an encapsulating reversal agent, will reduce opioid administration and subsequently postoperative respiratory events.*

The rationale for this project is to seek new knowledge regarding modifiable risk factors in anesthetic management. We expect findings from our proposal to allow the field to move vertically as there is currently limited knowledge regarding different anesthetic regimens and their impact on postoperative respiratory events. Once this knowledge is gained and if our hypothesis is not rejected, we can incorporate our findings as standard of care to improve safety, decrease unnecessary postoperative admissions, and reduce resource and cost utilization. Our hypotheses are as follows:

Primary Efficacy Objective – Our *working hypothesis* is that high-risk children having AT with neuromuscular blocks and reversal with sugammadex will have lower opioid consumption compared to children having AT without muscle relaxation.

Secondary Objectives – Our *working hypothesis* is that high-risk children having AT with neuromuscular blocks and reversal with sugammadex will have 1) decreased postoperative respiratory events and 2) fewer postoperative low MV episodes compared to those having AT without muscle relaxation.

At the completion of the proposed research, we expect to demonstrate a reduction in opioid consumption (Primary Efficacy Objective) and therefore

	respiratory events (Secondary Objective) after AT in high-risk children by adding neuromuscular blockade and subsequent reversal with sugammadex to our anesthetic management. The expected outcomes collectively attain our overall objective for the proposal by supporting the notion that certain modifications to the anesthetic regimen decrease the incidence of respiratory events after AT in high-risk children. These results are expected to have an important positive impact because they will provide strong evidence through a randomized controlled trial that an alternative anesthetic technique aimed at reducing opioid consumption reduces respiratory events after AT. This will provide new opportunities to mitigate the risk of these events that contribute to increased morbidity and cost and resource utilization after this commonly performed surgery.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	*A brief presentation should be made of the reasons for conducting the clinical study based on current knowledge of the product and /or disease state so that the study is presented in the proper perspective. Include the rationale for conducting the study and selecting the dose(s). Selected literature references critical to the study design, dosage selection, or rationale for the study should be cited, as appropriate. Studies using marketed products must cite the currently approved package circular for the product(s) (for the appropriate country) and the package circular may be included as an appendix.* ***Background, Rationale, and Preliminary Data*** AT is one of the most performed surgeries in children in the US. Most tonsillectomies in children are performed for treatment of OSA.[7] If left untreated, pediatric OSA leads to significant neurodevelopmental impairments and even cardiac dysfunction in the most severe cases. The risk of postoperative respiratory events such as severe airway obstruction, hypoxemia, and respiratory depression are high, with up to 46% of tonsillectomies resulting in such events.[2] There have even been reports of deaths following AT due to respiratory events.[8, 9]

Even though AT surgeries are performed to improve airway obstruction, pediatric AT patients have an increased risk of significant airway obstruction and other respiratory complications after surgery. There are likely several mechanisms responsible for this risk, primarily related to residual effects of anesthesia and opioid analgesics. Several postulated mechanisms exist for opioid-induced respiratory depression, which is heightened in children with OSA.[10, 11] Altered morphine pharmacokinetics are also apparent in children with OSA, particularly those with obesity and OSA, leading to higher peak intravascular morphine concentrations compared to control patients.[12] Other mechanisms which lead to respiratory events following AT include copious nasal secretions, reactive edema in the adenoid and tonsillar beds, and anatomical and physiological factors that cause upper airway collapsibility and obstruction that remain after AT.[11, 13-15] Postoperative respiratory events are a major source of morbidity, mortality, and cost/resource utilization following a relatively simple surgery in otherwise relatively healthy children.[3, 8, 9] Because of the high risk of postoperative respiratory events, without evidence regarding risk mitigation strategies, overnight admission for respiratory monitoring in high-risk children is recommended; however, the costs for these admissions is high for both families and medical systems.[3, 5] Further, society guidelines indicate a need for more research in this area.[5] Existing research has focused on risk associated with non-modifiable factors like age, severity of OSA, and comorbidities.[3, 4] There is substantial uncertainty to actual risk factors, as this work is almost entirely retrospective with major limitations in identification of the nature and severity of postoperative respiratory events. Risk prediction based on non-modifiable factors is useful, but optimum care for children requires development of risk-reducing interventions. Therefore, there is a *critical need* to identify strategies to prevent respiratory events after AT in children. If we are unable to meet this need, children will remain at high risk for adverse outcomes after AT, and healthcare system utilization and costs will remain high.

Despite hundreds of studies focused on *prediction* of respiratory events after AT, very few have examined prevention. A study that randomized children to preoperative albuterol or placebo found a reduction in postoperative respiratory events with albuterol. However, the respiratory events components measured were largely mild and self-limited, and not the type of events that typically lead to continued overnight respiratory care or monitoring.[16] Another trial found that premedication with intranasal dexmedetomidine decreased the risk of postoperative respiratory events compared to premedication with either intranasal midazolam or placebo. However, this study did not clearly delineate how events were measured, did not offer a biologic plausibility for the protective effect of intranasal dexmedetomidine, and the comparator (midazolam) was administered by a nonstandard route.[17] We collected *preliminary data* on 60 high-risk children after AT to identify modifiable risk factors for postoperative respiratory events. These data were collected prospectively with extremely granular outcome measurements obtained through respiratory volume monitoring and 0.5 Hz hemoglobin saturation values. We found opioid consumption increased the risk of hypoxemia after AT (**Table 1**) and extubating from a deep plane of anesthesia

Table 1. Results of stepwise Poisson regression analysis for predicting the number of episodes of hypoxemia (SpO2 < 90% for at least 10 sec) in the postanesthesia care unit following adenotonsillectomy in high-risk children

Variable	Estimate (95% CI)	P value
Age, years	0.87 (0.79, 0.97)	**0.01**
Postoperative oral morphine equivalents, mg/kg	1.19 (1.05, 1.34)	**0.01**
High-risk criteria		
Obesity (reference)		
Age	1.1 (0.52, 2.32)	0.78
Severe obstructive sleep apnea	0.86 (0.47, 1.59)	0.65
2+ reasons	0.34 (0.15, 0.75)	**0.01**
Preoperative opioid consumption	1.57 (0.87, 2.82)	0.13
Nasopharyngeal airway placement prior to extubation	2.49 (1.52, 4.08)	**<0.001**

Obesity = body mass index > 98th percentile; severe obstructive sleep apnea = apnea-hypopnea index > 10 events per hour

increased the risk of low MV events (**Table 2**). Specifically, we found that for every 0.1 mg/kg of oral morphine equivalents received, the number of episodes of hypoxemia (defined as SpO2 < 90% for at least 10 seconds) in the post-anesthesia care unit (PACU) increased by a factor of 1.19 (95% CI 1.05-1.34). We also found that extubating from a deep plane of anesthesia increased the number of low MV events by 1.49 (95% CI 0.97, 2.29). We conclude from the data that strategies targeted to decrease opioid consumption and depth of anesthesia at extubation will decrease risk of postoperative respiratory events.

Table 2. Results of stepwise Poisson regression analysis for predicting the number of episodes of low minute ventilation events in the postanesthesia care unit following adenotonsillectomy in high-risk children

	Estimate	95% CI	P value
BMI Z score			
<-1	3.91	1.49, 10.23	**0.01**
-1 to 0	0.46	0.20, 1.08	0.08
0 to 1	Reference		
1 to 2	2.04	1.20, 3.48	**0.01**
>2	1.04	0.57, 1.90	0.89
Reason for admission			
Obesity	Reference		
Severe obstructive sleep apnea	0.52	0.23, 1.18	0.12
Age	1.52	0.75, 3.08	0.24
2+ reasons	1.29	0.81, 2.05	0.27
American Society of Anesthesiologists Physical Status Score			
II	Reference		
III	0.56	0.36, 0.87	**0.01**
Comorbidity			
None	Reference		
Obesity	1.23	0.61, 2.45	0.55
*Other	1.39	0.77, 2.50	0.27
2+ conditions	1.96	1.11, 3.46	**0.02**
Extubated			
Awake	Reference		
Deep	1.49	0.97, 2.29	0.07

Twenty-six variables were included in the initial model. McFadden's R squared of the final model = 0.256. Other conditions include Trisomy 21, asthma, seasonal allergies, prematurity, seizure disorder, and autism.

Significance of Selected Topic

Our contributions here are expected to provide evidence of a benefit of an anesthetic regimen utilizing neuromuscular blockade to spare anesthetic and opioid agents. These contributions will be significant because they are expected to provide a change in the standard of care of anesthetic management of pediatric AT. This change can ultimately result in increased safety and reduced costs and resource utilization due to postoperative hospitalizations for the hundreds of thousands of these cases performed annually. We expect the prevention of respiratory events to reduce morbidity, and once these anesthetic and analgesic regimens are adopted on a wide-scale basis, to result in fewer postoperative admissions for respiratory monitoring, resulting in substantial costs and resource savings.

2.3 Study Design

This section is a concise overview of the study design stating the type of experimental design (observational or interventional; randomized block, crossover, etc.); whether the study is controlled (treatments other than the test product and/or placebo); whether the study is open or blinded/masked (single blind or double blind); the number of study centers (single or multicenter). The total number of patients included in the study and how they will be assigned to treatment groups must be indicated. When appropriate, state if the patients will be stratified. The procedures must be clear and concise. A description of the specific patient population to be studied should be stated. Both inclusion and exclusion criteria should be listed and should be consistent with the current product label.

If the study is intended to be observational then the protocol needs to state this and the expectations are different since most observational studies are database studies,

retrospective, aggregate studies as opposed to open label studies for efficacy and safety.

This will be a randomized, patient- and assessor-blinded, parallel arm, controlled trial assessing the efficacy of neuromuscular blockade with reversal during the anesthetic management of pediatric AT to reduce intra- and postoperative opioid consumption and postoperative respiratory events in high-risk patients. Enrolled subjects will be randomized by computer-generated assignment using stratified blocked randomization with a 1:1 allocation into 2 arms: neuromuscular blockade with reversal at the end of surgery and no neuromuscular blockade. Randomization will occur on the following strata: severe versus non-severe OSA/sleep disordered breathing. Patients/families, treating teams (except for the anesthesia team), and research staff/investigators responsible for measuring and adjudicating outcomes will be blinded to allocation.

If there is an error or outage in the REDCap-generated randomization tool, the team will randomize using an online random number generator (1, 2 with 1 equaling neuromuscular blockade and 2 equaling no neuromuscular blockade). The allocation will be recorded, and the team biostatistician will be notified. We will resume use of the REDCap allocation table without modification or consumption of allocations for ensuing enrollments once REDCap is again functional.

Subject recruitment: We will recruit a consecutive sample of 172 consenting patients over a 1-year period. Patients will be recruited from the Children's Health main Dallas campus, a large freestanding tertiary care pediatric hospital in an urban setting. Children's Health has the necessary case volume to support this research. In 2022, 443 high-risk tonsillectomies were performed at the main Dallas campus, of whom we propose to recruit 39% in one year. **Table 3** shows inclusion and exclusion criteria. Our high-risk patient population represents a racially and ethnically diverse background with over 70% of patients identifying as non-white.

Table 3. Inclusion and exclusion criteria

Inclusion criteria
-Children 2-12 years of age having tonsillectomy with or without adenoidectomy at Children's main Dallas campus
-Considered high-risk* with pre-planned overnight admission after surgery for respiratory monitoring
Exclusion criteria
-Planned placement on positive airway pressure or supplemental oxygen postoperatively
-Secondary procedures under the same anesthetic, except for myringotomy tubes or auditory brainstem response testing
-Children with neuromuscular disorders such as congenital myopathies, myotonias, or myasthenia gravis
-Known rocuronium, vecuronium, or sugammadex allergy
*High-risk children have any one of the following characteristics: age < 3 years, severe obstructive sleep apnea (apnea-hypopnea index > 10 events per hour), or obesity (body mass index > 98th percentile).

Feasibility: Our team has the necessary experience and skill to carry out this proposed project. I successfully recruited patients from this cohort for an observational study to obtain preliminary data. Although this study was observational, our enrollment rate was 98%. Our team is also currently recruiting a more restrictive cohort of pediatric tonsillectomy patients with severe OSA only for another observational study to predict overnight respiratory events after surgery. Between 6/8/2023 and 8/18/2023, we recruited 50 of 53 eligible patients. Our research team has a proven track record with successfully completing clinical trials, with a > 90% enrollment and retention success rate. For the proposed study, we only require a recruitment rate of ~39% during the 1-year award period. We are currently the highest-ranking site for recruitment in the T-REX trial, a trial assessing the impact of a low-dose volatile anesthetic on neurodevelopmental outcomes. There are 20 participating sites, and we have enrolled 20% of the subjects. We have met enrollment goals in 100% of the studies conducted by our team in the last five years. Although the proposed study is a randomized clinical trial, we anticipate high enrollment rates because the study intervention is commonly employed during

pediatric anesthesia management. We will include this information in the consent process. To ensure acceptability of the study procedures and minimize protocol violations, treating anesthesiologists will be study team members. We have a core group of investigators in our Division with a history of publishing research together.[18-20] We often advise and work together on projects to ensure successful study conduct. This group is an invaluable resource and another aspect that supports feasibility of this project.

Our study team is confident in our ability to complete the study by the end of 2024 and we are already planning for this goal. We submitted the proposed study to the UT Southwestern Institutional Review Board (IRB) on 08/22/2023. Approval typically requires 4 weeks. In addition, the Children's Health Performance Site approval process proceeds in parallel with IRB review.

Study conditions: The anesthetic regimen will be standardized and controlled to reduce the effects of co-interventions that may impact the outcomes. The controlled anesthetic is nearly identical to an enhanced recovery after surgery protocol used at our center. See "Study Procedures" for full anesthetic plan. Following anesthesia induction and placement of an intravenous catheter (IV), patients randomized to neuromuscular blockade will receive 0.6 mg/kg of rocuronium and those randomized to standard care will not. Quantitative neuromuscular monitoring will be utilized to determine the dose of sugammadex reversal at the conclusion of the case.

The treating anesthesiologist for each study case will be a listed study team member to help streamline the execution of the standardized anesthetics. All treating anesthesiologists will be designated as study team members and will undergo training, during which the Principal Investigator will review the standardized anesthetic approach. The training will emphasize the importance of minimizing bias associated with anesthetic groupings.

All cointerventions which may influence the contribution of intraoperative opioid consumption to the primary outcome will be limited through the controlled conditions of the anesthetic. Specifically, agents with analgesic properties such as nitrous oxide, ketamine, and dexmedetomidine above the standardized dose will be prohibited. This will limit bias by the treating anesthesiologists such that when analgesic medications are indicated during surgery, opioid will be standardly administered and selective administration of more or less fentanyl to either study group will be avoided.

Rigor and reproducibility: The primary strengths of the preliminary data that serve as the basis for this proposed project include the following: 1) the data were sampled from the same population of high-risk children and 2) the outcome measurement of hypoxemia was observer measured by trained study staff in addition to 0.5 Hz hemoglobin saturation values to measure episodes of hypoxemia accurately and precisely. Our preliminary data also provided an estimate of the mean and standard deviation of cumulative intra- and postoperative opioid consumption in this cohort, which forms the basis of our sample size determination for this proposed project. Postoperative respiratory events will be measured with a more accurate and valid approach compared to respiratory event measurement in prior studies, where it was narrowly defined and primarily measured by chart review. We adhered to the SPIRIT and CONSORT guidelines in the writing of the approach/protocol to help ensure the experimental design and methods will achieve robust and unbiased results. We factored relevant biological variables such as sex, age and race/ethnicity into the design and analyses. Studies indicate males, children under the age of 3 years, and black children are at higher risk of respiratory events following AT.[3, 7, 21] The trial will be randomized, and we expect equal allocation of sex and

	race/ethnicity. However, regression analyses will factor these important baseline covariates. Additionally, the experimental design allows for disaggregation of data so results obtained from groups of children could be analyzed separately and compared. We plan a process of pretesting recruitment, measurement, intervention, and data collection plans to avoid protocol revisions after study start. One of the secondary outcome measurements will utilize a novel, FDA-approved, non-invasive respiratory volume monitor (RVM) to measure low MV events. This monitor is authenticated to measure respiratory rate and tidal volume and is FDA-approved for the monitoring of breathing in children. To ensure accuracy and precision of all outcome measurements, we will utilize a study operations manual to standardize procedures and rigorously train study staff. We will ensure that study staff can demonstrate competence in the clinical procedures prior to study start. We will also limit the number of staff with these responsibilities to ensure accuracy and precision.
2.4 Diversity & Inclusion	*Please explain how the study would support diversity in access to enrollment and inclusion of people of varying age, race, ethnicity, and gender reflecting the patient population that is affected by the disease/condition being studied.* Our high-risk AT population represents a racially and ethnically diverse background with over 70% of patients identifying as non-white. We will utilize in-person interpreters for Spanish-speaking subjects and virtual interpreters for non-English, non-Spanish speaking subjects**.** We will also utilize translated Spanish consent forms. Recruitment will be attained through screening of potentially eligible subjects by study staff, which we expect will control against the inequality in access to participation that is a risk when recruitment of potential subjects relies on volunteering.
2.5 Patient Engagement	*Please explain if the study design, recruitment and conduct will be informed by a patient or patient advocate.* The study has not been informed by a patient or patient advocate.
2.6 Study Flowchart	*A study flow chart is highly recommended. It should display all clinical and laboratory measurements and the time periods (e.g., hours, days, weeks) at which data are to be collected.* Please see the end of this document for the study flowchart.
2.7 Study Procedures	*This section is a detailed explanation of the experimental design. The use of subheadings, lists, tables, or outlines are recommended. Describe the initial screening period(s), baseline period(s), treatments to be compared, study configuration (parallel, crossover, etc.), duration of the treatment period(s), control group(s), follow-up procedures, and length of time specified for washout intervals and safety follow-up. In protocols that specify a screening or washout period, indicate that once a patient signs a consent form, a unique number (screening or baseline number) should be assigned for identification purposes. It should be noted that that under no circumstances should a patient be assigned more than one allocation number* *How subjects will be recruited.* We will identify eligible subjects through daily screening of the surgery schedule**.** We will place a preoperative phone call three business days before surgery to inform parents of the study and give advance notice that we will be approaching for potential enrollment. We will approach patients and their families in the preoperative area and obtain written informed consent from those willing to participate. Members of the study team will have a treatment relationship with potential subjects. Children enrolled in the study will have a treating anesthesiologist who is a member of the study team. *Description of informed consent, parental permission, and assent*. Voluntary informed consent will be obtained from all subjects' parents or guardians prior to initiating any study-related procedures or assessments for the proposed project. Written informed consent will describe: the voluntary nature of the study, the purpose

of the study, inclusion criteria, randomization and study procedures, conditions for early stoppage of the study, risks of participation, steps to be taken if research related adverse events occur, benefits of participating, alternatives to participating, and confidentiality procedures. It will also provide contact information of the principal investigator. We will obtain signed assent from typically developed children 10 years of age and older**.** We will utilize in-person interpreters for Spanish-speaking subjects and virtual interpreters for non-English, non-Spanish speaking subjects**.** We will also utilize translated Spanish consent forms.

Study procedures. The anesthetic regimen will be standardized and controlled to reduce the effects of co-interventions that may impact the outcomes of interest. The controlled anesthetic is like an enhanced recovery after surgery protocol already in place for AT at our center. Patients will receive oral midazolam 0.5 mg/kg (maximum dose 15 mg) and oral acetaminophen 15 mg/kg (maximum dose 800 mg) as a pre-medication 20-30 minutes prior to surgery. A BIS monitor will be applied to the forehead and anesthesia will be induced by mask inhalation with 8% sevoflurane in 100% oxygen, following which an IV will be placed. Quantitative, EMG based, neuromuscular monitoring electrodes will be applied to the posterior tibial nerve in children weighing less than 20 kg and to the ulnar nerve in children weighing more than 20 kg in those randomized to receive neuromuscular blockade. Dexmedetomidine 0.3 mcg/kg (maximum dose 12 mcg) will be given intravenously. Patients randomized to receive neuromuscular blockade will receive 0.6 mg/kg rocuronium (maximum dose 50 mg), and then intubated when the train of four count is zero. Patients randomized to standard management will be intubated following dexmedetomidine administration. The RVM will be applied and synced to invasive MV measurements from the anesthesia ventilator following intubation. All patients will receive intravenous dexamethasone at a dose of 0.5 mg/kg (maximum dose 8 mg). Anesthesia will be maintained with sevoflurane and titrated to maintain BIS between 40 and 60 in both study groups. If the BIS value rises above 60 in either group, the expectation will be that the sevoflurane concentration will be increased until the BIS decreases below 60. Administration of fentanyl will be at the discretion of the attending anesthesiologist. Opioid analgesics other than fentanyl will be prohibited. Intraoperative administration of the following drugs with analgesic properties will also be prohibited: nitrous oxide, acetaminophen, ketorolac, and ketamine. Propofol administration will be prohibited except for cases of life-threatening movement or to treat airway hyperreactivity defined as laryngospasm, bronchospasm, or severe coughing episodes. Additional doses of rocuronium at a dose of 0.2 mg/kg (maximum dose 15 mg) will be administered when neuromuscular monitoring indicates a train of four count is 2 or greater to patients randomized to receive neuromuscular blockade. When the surgery is completed, sugammadex will be administered to patients randomized to receive neuromuscular blockade. Sugammadex 2 mg/kg will be administered if the train of four count is 2 or greater. Sugammadex 4 mg/kg will be administered if 1) the train of four count is 1, or 2) if the train of four count is 0 and the post tetanic count is at least 1 (no maximum dose). Ondansetron 0.1 mg/kg (maximum dose 4 mg) will be given intravenously. Patients in the neuromuscular blockade group will be extubated when the train of four ratio is at least 90%. All patients will only be extubated when awake. Awake extubation will be defined as the presence of 3 of the following: facial grimace, purposeful movement, conjugate gaze, eye opening, and tidal volume greater than 5 ml/kg.[22]

At our institution, children standardly receive supplemental oxygen by blowby facemask after extubation. This oxygen supplementation will be removed once the child arrives to PACU. Respiratory events will be measured during the entire PACU stay. Postoperative administration of analgesic medications will be standardized. Patients will be screened for pain in the PACU and will receive nurse-administered intravenous fentanyl 0.5 mcg/kg (maximum dose 25 mcg) for a score of 4 or greater on age-appropriate pain scales. If three doses of fentanyl are insufficient to control pain, the next course of action will be at the discretion of the PACU

anesthesiologist and/or the anesthesiologist for the case. Oral ibuprofen will be administered at a dose of 10 mg/kg (maximum dose 500 mg) every 6 hours and oral acetaminophen will be administered at a dose of 15 mg/kg (maximum dose 800 mg) every 6 hours, alternating with ibuprofen. Patients will be screened for pain on the postoperative ward, with standard assessments every 4 hours. Nursing staff will contact the surgical resident or advanced practice provider for persistent pain scores of 4 or greater, at which time a dose of oral oxycodone 0.05 mg/kg, and/or additional daily doses of dexamethasone may be considered.

All children considered high-risk, and therefore all patients in the proposed study, are admitted for overnight observation following AT. If no respiratory concerns present overnight, children are typically discharged between 0900-1200 the morning following surgery. Therefore, depending on the scheduled surgery start time, all children are observed between 15 and 23 hours following surgery. It is exceedingly rare at our institution for children to be discharged home with a prescription for an oral opioid analgesic following AT, so we anticipate all opioid consumption will occur during the study observation period.

Description of data collection and management responsibilities. Subject files will be maintained including the signed Informed Consent, HIPAA Authorization, and copies of subject source documentation. They will be stored in a secure, locked cabinet. Deidentified clinical data will be entered into REDCap, a password-protected data capture system provided by the University of Texas Southwestern Medical Center (UTSW). Clinical data will be entered directly from the source documents. Data will be collected for research purposes only. Study records acquired during this research study will be saved for at least 5 years after study completion. In accordance with the NIH's Data Management Sharing Policy and recent focus in the scientific community on data sharing, deidentified data will be stored in the UTSW Data Repository, an open access data repository for researchers affiliated with UTSW.

List of the study intervention being tested under this protocol. The study intervention being tested is the administration of rocuronium with subsequent reversal during anesthesia in high-risk children having tonsillectomy.

Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol. The study intervention being tested is the administration of rocuronium with subsequent reversal. Only patients randomized to the treatment arm will receive this intervention. Benefits of receiving this intervention include possible reduced opioid consumption, which our preliminary data suggest may decrease respiratory adverse events after tonsillectomy.

All other research procedures not listed in "Risk:Benefit Analysis" above.

#	Research component • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	Column A **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	Column B **Research <u>Only</u>** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*
1	**Study Procedures**		
	Placement of neuromuscular monitoring sensor and neuromuscular monitoring		1
	Rocuronium administration		1
	Intubation	1	
	Placement of respiratory volume monitor padset and monitoring		1
	Placement of BIS monitor probe and monitoring		1
	Maintenance of anesthesia with sevoflurane	1	
	Sugammadex administration		1
	Extubation	1	
2	**Outcome assessments**		
	Intraoperative opioid consumption	1	1
	BIS measurements		1
	Measurement of time from procedure complete until out of OR	1	1
	PACU pain assessments (Wong Baker, revised Face, Legs, Activity, Cry, Consolability, or numeric pain ratings as age appropriate)	1	1
	Postoperative opioid consumption	1	1
	Postoperative respiratory adverse events screening	1	1
	PACU respiratory volume monitoring		1

	Measurement of time in PACU until PACU discharge criteria are met	1	1

Safety precautions

Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

All dosing of rocuronium and sugammadex will be weight based. Further safety is introduced by using quantitative neuromuscular monitoring to guide dosing. Patients will also be screened for and excluded if they have known allergies to either medication or risk of compounded intrinsic weakness with rocuronium due to underlying conditions.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Subjects will be under the direct care of an anesthesiologist during and after administration of study drugs. If any adverse events occur, the anesthesiologist will be ready and capable of intervening as appropriate.

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No

If yes, describe here

2.8 Study Duration

Estimate the length of time (e.g., number of days, weeks, months) required to recruit patients and complete the study.

In 2022, 443 high-risk tonsillectomies were performed at the main Dallas campus, of whom we propose to recruit 39% in one year. We are currently enrolling children with severe OSA having AT for a prospective observational pilot study to determine the feasibility of utilizing the RVM to predict overnight respiratory events. That cohort is a more restrictive sample compared to the cohort in the study proposed here (children with severe OSA only versus children with any of the following criteria: age less than three years, obesity, or severe OSA). Our average enrollment rate has been 5 subjects per week for our current pilot study (50 patients enrolled between June 8 and August 18). Considering that enrollment rate is for a more restrictive sample of patients, *at a minimum*, we anticipate meeting that enrollment rate of 5 subjects per week. This would result in an enrollment rate of 20 subjects per month, allowing us to meet our intended sample of 172 patients within 9 months. Again, this is an estimated *minimum* enrollment rate considering the eligible cohort for the proposed study will be much larger. **Table 4** outlines the estimated timeline.

TABLE 4. TIMELINE AND BENCHMARKS FOR SUCCESS

AIMS/TASKS	YEAR 01			
Primary Efficacy Objective				
Recruit patients				
Analyze opioid consumption				
Secondary Efficacy Objective				
Recruit patients				
Analyze postoperative respiratory events and low MV events				
Deliverables				
Preliminary abstract				
Manuscript preparation				

2.9 Statistical Analysis and Sample Size Justification

State who will be responsible for analyzing the study data (Investigator, contract CRO, etc.). When appropriate state how the blind will be maintained during the study, as appropriate, and when the data will be unblinded. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed, protocol violators have been identified (if appropriate), and data has been declared complete.

The statistician, who is a study investigator, will be responsible for analyzing data. Blinded investigators will not be unblinded until medical/scientific review has been completed, protocol violators have been identified (if appropriate), and data has been declared complete. Research team staff not responsible for measuring/adjudicating outcomes will carry out randomization and group allocation.

Variables/Time Points of Interest

All variables (primary and secondary) that are listed in the study hypotheses, and the time points at which they will be analyzed, need to be described in detail.

Efficacy variables discussed in this section should have been included as part of an objective or hypothesis section. These variables and the time points at which they are to be analyzed should be consistent with the primary and secondary hypotheses, i.e., primary variables and time points should relate to the primary hypotheses.

Primary efficacy objective - Cumulative intra- and postoperative opioid consumption will be measured by chart review as a continuous outcome. All opioid received during the intra- and postoperative period up to 24 hours after surgery or discharge home will be summed and converted to intravenous morphine equivalents and normalized to body weight (mg/kg).

Secondary objectives - Postoperative respiratory events will be measured as a composite binary outcome consisting of 1) airway obstruction or hypoxemia, defined as SpO2 <90%, requiring any of the following interventions: supplemental oxygen by nasal cannula or simple face mask, noninvasive positive airway pressure, or reintubation; or 2) unanticipated ICU admission. We will measure respiratory events for 24 hours postoperatively or until discharge home. PACU measurements will be by continuous, direct, bedside observation by trained study staff. Postoperative respiratory events on the ward will be measured by a questionnaire administered to the patient's bedside nurse. We will administer a questionnaire to the dayshift nurse at end of shift (1900 hours) and to the nightshift nurse at end of shift (0700 hours). We may discontinue monitoring for respiratory events after 0700 if no respiratory events occurred overnight.

Low MV events will be defined as MV < 40% predicted for at least 2 minutes and measured by the RVM (ExSpiron®2Xi, Respiratory Motion Inc, Watertown, MA) as a count outcome. Predicted MV is calculated by the RVM based on body surface area. The RVM will be applied and synced to invasive MV measurements from the anesthesia ventilator following intubation. MV will be measured continuously in the PACU, and monitoring will be discontinued upon transfer to the postoperative ward. Bedside staff will be blinded to RVM parameters.

We have experience with the RVM in 2 prior studies. In a study where we used the RVM overnight to monitor minute ventilation in children with severe OSA on the first night after tonsillectomy, roughly 10% of our sample of 60 had sufficient data loss such that the outcome of low MV events could not be measured or analyzed. This data loss was primarily related to noncompliance with the chest wall padset in young or developmentally deficient children, or related to insufficient battery power in instances where the device was inadvertently left unplugged from a power outlet. We expect these issues to be minimal in the proposed study. The RVM will be used to monitor MV only during the PACU stay, where the child and the device will be under direct and continuous observation by study staff, and any potential issues can be immediately addressed. In fact, in the other study we conducted using the RVM during the PACU stay in children after tonsillectomy, we did not have any data loss. Additionally, the RVM measurements will be directly downloaded from the device using a USB drive. We will personally analyze the measurements and adjudicate the outcome of low MV events using statistical software code written by this proposed study's statistician for a prior study.

Additional objectives - We will also measure the following outcomes 1) time from procedure completed until the patient is out of the operating room as a continuous outcome with a measurement variable of minutes, 2) time in the PACU until post-anesthesia discharge criteria are met as a continuous outcome with a measurement variable of minutes, and 3) BIS values.

Statistical Methods

All planned primary analyses and key secondary analyses should be discussed in this section. If other secondary and tertiary analyses are planned, then a statement should be included in this section as to what these analyses are.

Describe in detail the statistical methods that will be used for the primary hypotheses or estimation. State the statistical tests which will be used (e.g., ANOVA, Kaplan-Meier) along with other important considerations (e.g., factors in ANOVA, pre-specification of covariates, strata for Mantel-Haenszel, use of historical controls).

Demographic and clinical characteristics for the sample of patients will be described using the sample mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. We plan an intention to treat analysis with a per protocol sensitivity analysis if protocol violations are encountered. A Generalized Linear Model approach will be implemented to address the study Aims. Linear regression (ANCOVA) will be used to model the mean of the continuous response variables, logistic regression will be used to model the odds of the binary response variables, and Poisson regression will be used to model the mean of the discrete response variables. All statistical analyses will be carried out using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

Primary efficacy objective - A mixed model analysis of repeated measures will be used to evaluate cumulative morphine equivalents between the neuromuscular blockade versus standard anesthetic groups over the intraoperative and postoperative time periods. The response distribution of morphine equivalents will be assessed for distribution specification in the mixed model (e.g., Gaussian, Poisson). The mixed model will contain fixed effects terms for Anesthetic Group and Anesthetic Group × Time interaction. Covariates will be considered for inclusion in the model. Restricted maximum likelihood estimation along with Type 3 tests of fixed effects will be used with the Kenward-Roger correction applied to the best fitting covariance structure. Least squares group means, and contrasts, will be estimated as part of the model to interpret the Anesthetic group effect. Simple Anesthetic group effects at each time period (intraoperative and postoperative) as well as within-group change from the intra- to post-operative periods will also be assessed. Cohen's *d* will be calculated and interpreted as the effect size estimator.

The sample size estimate is based on the primary outcome of cumulative intra- and post-operative morphine equivalents. Using the repeated measures design (2 between- and 2 within-subjects) along with a linear mixed model—contrasts of means, tests of regression coefficients—and a total of 172 evaluable participants (86 per group), we estimate statistical power of 90% to detect an effect size as small as f=0.25, attributable to any single contrast, based on an overall alpha level of 0.05. The stated effect size is considered from the expected minimal important difference of 0.05 mg/kg of intravenous morphine equivalents between the two groups with a SD of 0.10 mg/kg. This minimal important difference is supported by prior studies examining the impact of the addition of non-opioid analgesics on opioid consumption in pediatric tonsillectomy.

Secondary objectives - Logistic regression, with penalized maximum likelihood estimation along with Firth's bias correction, will be used to estimate the odds of

postoperative respiratory events between the two anesthetic groups in the PACU and postoperative ward. Covariates (e.g., age, sex, ASA status, OSA severity) will be considered for inclusion in the model. The odds ratio will be interpreted as the effect size estimator for the treatment effect. As a sensitivity analysis, a mixed model analysis of repeated measures similar to that mentioned above will also be implemented to evaluate respiratory events between the neuromuscular blockade versus standard anesthetic groups over the PACU and postoperative ward phases.

A Poisson (or negative binomial) regression, within a Generalized Estimating Equation framework, will be used to compare the number of postoperative low MV events between the neuromuscular blockade versus standard anesthetic groups. The relevant covariates will be considered for inclusion in the model. Maximum likelihood estimation and robust standard errors (Huber Sandwich Estimator) along with Type 3 tests of fixed effects will be used with the Wald Chi-Square statistic. The Poisson model will be checked for overdispersion. The response rate ratio will be calculated and interpreted as the effect size estimator for the treatment effect.

Additional objectives - ANCOVA will be used to evaluate each of the additional continuous outcomes (e.g., time from procedure complete until patient out of operating room, time in the PACU until post anesthesia discharge criteria are met, and BIS values) between the neuromuscular blockade versus standard anesthetic groups. A log-linear model (via a lognormal distribution) will be considered if the continuous outcomes depart from normality. Nonparametric ANCOVA will also be considered if the statistical assumptions of the parametric ANCOVA are not tenable.

The following covariates will be adjusted for in final analyses: age, sex, race, OSA severity (mild, moderate, severe) in children with a preoperative polysomnogram, active or recent upper respiratory tract infection in the past 4 weeks, history of extreme prematurity less than 28 weeks of gestation, Trisomy 21, and obesity defined as BMI greater than 98th percentile for age and sex.

Multiplicity

If appropriate, describe the multiplicity approach to support the statistical conclusions of the trial.

The level of significance will be set at α=0.05 (two-tailed) and the False Discovery Rate procedure will be used to control false positives over the multiple tests.

Power/Sample Size:

In studies with hypotheses, minimally, for the primary endpoint of the study, a power statement needs to be included to show the detectable difference relative to the primary hypothesis. For example, the following level of detail is expected:

Based upon a sample size of n=40 patients per group, this study has 80% power to detect a 5.4 mmHg difference between groups in systolic blood pressure; this calculation is based on a between subject standard deviation of change of 9 mmHg for systolic BP (reference for where this variability statement originated).

In estimation studies, the precision of the primary/secondary estimations needs to be given with the sample size of the trial.

The sample size estimate is based on the primary efficacy objective (cumulative intra- and postoperative opioid consumption). In our preliminary data, the SD of cumulative intravenous morphine equivalents received was 0.08 mg/kg. To be conservative, we used an SD of 0.1 mg/kg. Assuming a minimal important difference

	of 0.05 mg/kg of intravenous morphine equivalents between groups, 86 patients in each of the 2 groups will provide a power of 0.9 using a t-test to reject the null hypothesis that there is no difference in mean opioid consumption. This minimal important difference is supported by prior studies examining the impact of the addition of non-opioid analgesics on opioid consumption in pediatric tonsillectomy.[23, 24]
2.10 Specific Drug Supply Requirements	*The following should be indicated in the study protocol or provided by the investigator:* *Include whether the drug supplies will be purchased locally as marketed product or if open label or blinded supplies will be required by MSD.* *Indicate whether your institution's pharmacy will require bulk supplies from MSD (one large container with tablets, capsules, etc.). If bulk supplies are provided by MSD, indicate if your institution's pharmacy will responsible for filling individual patient containers, labeling the containers and performing the blinding of the supplies. A description as to how the clinical supplies are to be packaged and labeled for each patient should be added to the protocol.* *If MSD is packing and labeling the containers, provide a translation of the label text and patient instructions in your native language.* *If a study is to be conducted in a country within the European Union and follows the EU Clinical Trial Directive, the EUDRACT number must be obtained by the investigator and provided to the MSD office.* *Note: At conclusion of the study or upon drug expiration, the MSD Scientific Leadership & Research Manager will be responsible for issuing a Drug Disposition Letter to the investigator for US based studies.* *For US and non-US studies, the investigator will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. Clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are dispensed in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study.* Open label drug supplies will be required from MSD. Bulk supplies will be required by our institution's pharmacy and the pharmacy will be responsible for dispensation of sugammadex vials to the operating room for use during study procedures.
2.11 Adverse Experience Reporting	*The study agreement outlines the requirement for adverse experience reporting. For clinical protocols, specific adverse experience reporting requirements must be identified in the protocol if the Model Study Agreement is not used (in general, this would apply to non-US. studies whose local requirements may prohibit the use of the agreement).*
2.12 Itemized Study Budget	*A preliminary study budget must be provided with the initial proposal submitted to give guidance to the MISP Review Committee as to the expected study costs. A refined itemized budget detailing the costs associated with the study should be provided with the final protocol or included in the study agreement as Exhibit B.*
2.13 References	*All literature references cited in the protocol should be listed accordingly in the reference section.* Please see references section at the end of this document.

2.14 Publication Plan	*Generally, a publication plan is discussed between the investigator and MSD /MSD during time when the protocol is under development. Details of the publication and the obligations to MSD are outlined in the study agreement.* *The following should be considered for the publication plan:* • *What are your publication plans? How many manuscripts do you anticipate?* • *Include projected target date for manuscript submission and name of the journal* • *Do you anticipate abstracts? How many?* • *What scientific meetings would you consider presenting the study results?* We anticipate one full manuscript from the conduct of this proposed research. The projected target date for manuscript submission is approximately 3 months following the completion of enrollment and data analysis, which we anticipate will occur in the fourth quarter of the one-year period of this proposed research. We plan to submit to *Anesthesiology*. We also anticipate one abstract with preliminary results in the third quarter of the one-year period of the proposed research. We would consider presenting the abstract at the American Society of Anesthesiologists Annual Meeting, as well as the Society for Pediatric Anesthesia annual Spring Meeting.
2.15 Curriculum Vitae	*Investigator should upload dated curriculum vitae in English with a listing of references to Visiontracker at:* *https://mrk.envisionpharma.com/ienv_mrk/visiontracker/portal/login.xhtml?pgm=ISR&windowId*
2.16 Protocol Submission for Investigator-Initiated Studies	*U.S. protocols should be submitted by US investigators directly to Visiontracker at* *https://mrk.envisionpharma.com/ienv_mrk/visiontracker/portal/login.xhtml?pgm=ISR&windowId* *Non U.S. protocols should be submitted to the MSD office by the investigators.*

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Study Flow Chart