Randomized Double---Blinded, Controlled Trial to Compare the Effectiveness of Sugammadex vs. Placebo to Prevent Residual Neuromuscular Block in the Post---Anesthesia Care Unit as Evaluated with a Non---Invasive Respiratory Volume Monitor

NCT02728726

6/29/2017

f

Merck Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	Randomized Double-Blinded, Controlled Trial to Compare the Effectiveness of Sugammadex vs. Placebo to Prevent Residual Neuromuscular Block in the Post-Anesthesia Care Unit as Evaluated with a Non-Invasive Respiratory Volume Monitor
Request Date:	Protocol Version date 6/29/17
Institution Name:	Mayo Clinic, Jacksonville University of Texas - UT Health, Houston
Investigator Contact Information:	J. Ross Renew, MD Assistant Professor of Anesthesiology Department of Anesthesiology Mayo Clinic 4500 San Pablo Rd. Jacksonville, FL 32224 O: 904-956-3328 E: Renew.J@mayo.edu Jaideep H. Mehta, MD The University of Texas, UTHealth Department of Anesthesiology 6431 Fannin Street, MSB 5.020 Houston, TX 77030 [redacted]

Section #2- Core Protocol

The Primary objective of this study is to determine whether patients who receive sugammadex immediately after tracheal extubation will exhibit a decrease in the incidence of postoperative residual paralysis and an associated decrease in the incidence of postoperative respiratory depression (which can precede critical respiratory events, CRE).

The Secondary objectives are to: a) determine whether patients receiving sugammadex will have a normal TOF ratio (>0.90) indicative of full neuromuscular recovery in the PACU; and b) to improve patient safety by documenting whether postoperative respiratory depression (decreased MV below 80% and 40% of predicted MV as assessed by a Respiratory Volume Monitor) is due to opioid administration vs. postoperative residual neuromuscular block (by comparing postoperative VAS scores and total opioid administered).

2.1 Objectives & Hypotheses

Hypotheses:

A. After routine care and reversal of neuromuscular block as per usual clinical routine, and after tracheal extubation, surgical patients randomized to receive sugammadex vs. placebo in the OR will:

1) have a lower incidence of "Decreased MV" [MV <80% MV predicted (MV_{PRED}) based on BSA] as well as lower average MV sustained at 15-30 minutes after PACU arrival than placebo patients

2) have a lower incidence of "Low MV" as well as lower average MV at PACU discharge. An instance of "low MV" occurs when the measured MV is <40% MV predicted (MVPRED) based on BSA, for any contiguous 10 minutes in the 30 minutes leading up to PACU discharge.

B. A smaller fraction of patients in the sugammadex group than in the placebo group spend more than 2 minutes in the PACU with a sustained "Low MV."

C. A smaller fraction of patients in the sugammadex group than in the placebo group spend more than 2 minutes in the PACU with a sustained "Low MV" when corrected for PACU length-of-stay (LOS).

D. The average %MV predicted is greater in the sugammadex group than in the placebo group.

E. PACU LOS is shorter in patients receiving sugammadex as compared with placebo patients.

F. Fewer patients in the sugammadex group have respiratory complications or require respiratory monitoring (O_2 desaturation, atelectasis, O_2 administration, CPAP, BiPAP, reversal medication).

	G. The sugammadex group has higher train-of-four (TOF) ratios than the placebo group at equivalent time points throughout their PACU stay. H. The ExSpiron is able to identify respiratory depression (defined as instances of MV <40% MV_{PRED} lasting at least 1minute occur prior to instances of SpO2 <90% lasting at least 2 minutes). **I.** Lower MV measurements (corrected for total morphine equivalents administered) are correlated with lower TOF ratios.

2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	**Background and Rationale** A. Sugammadex Background. Sugammadex is a relatively new compound, a gamma-cyclodextrin molecule that forms an 8-membered ring. Its internal ring diameter of approximately 7.4 A is just sufficiently large to accommodate the external diameter of the aminosteroidal nondepolarizing neuromuscular blocking agents (NMBAs) rocuronium, vecuronium and pancuronium (in decreasing binding affinity).[1] The sugammadex-NMBA (rocuronium) complex has a very high affinity (association constant), such that once encapsulation of rocuronium by sugammadex occurs, dissociation is nearly non-existent. When administered to patients who received rocuronium-induced neuromuscular block, sugammadex binds free plasma rocuronium irreversibly, lowering the plasma concentration of free rocuronium. This promotes diffusion of free rocuronium from the neuromuscular junction back into the plasma, where the free rocuronium is again encapsulated. This removal of rocuronium from the neuromuscular junction reverses the neuromuscular block more rapidly and effectively than traditional anticholinesterases (neostigmine). Sugammadex is devoid of the side effects associated with neostigmine administration, and no anticholinergics (glycopyrrolate) need to be co-administered.[2] Sugammadex can reverse a rocuronium neuromuscular block of any depth, depending on the administered dose. Its time to complete reversal is also dose- dependent, but it averages 2-4 min, as opposed to reversal with neostigmine that requires 10-40 min for complete reversal. Sugammadex has been FDA approved for clinical use in the US. Sugammadex does not bind to most other anesthetic drugs or endogenous steroids, and has no affinity for any known receptors. It does bind to oral contraceptives and some rare antibiotics. There have been very few reported adverse events associated with sugammadex use, such as allergic reactions. [3]

B. Respiratory Volume Monitoring (RVM) Background:

An non-invasive RVM (ExSpiron, Respiratory Motion, Inc., Waltham MA) based on thoracic electrical impedance been shown to accurately monitor respiratory status in non-intubated patients, providing a real-time respiratory curve and measurements of minute ventilation (MV), tidal volume (TV) and respiratory rate.[4,5,6,7,8] The ExSpiron system consists of two main components, a monitor and an electrode PadSet, which utilizes 3 adhesive electrode patches placed on the thorax, similar to ECG monitoring electrodes.

Simultaneous measurements of MV, TV, and RR with the RVM and a Wright monitoring spirometer demonstrated a precision error of 7.2% and 7.1% for MV and TV, and an accuracy error of 9.3% and 9.0%, respectively. Throughout the range of 4 breaths per minute (bpm) to 40 bpm and during erratic breathing, RVM measurements were highly correlated with measurements made with a Morgan diagnostic spirometer ($r = 0.96$, 95% CI: 0.93 to 0.99).[9]

In a recent study at the Massachusetts General Hospital in Boston published in the Journal of Trauma,[10] the RVM evaluated 132 PACU patients following elective joint replacement surgery under general or regional anesthesia. This work demonstrated the effects of opioids on RVM measurements, and a stratification based on opioid sensitivity was proposed. This finding is relevant to the study proposed here, because the following categories were defined: "At-Risk" was defined as patients with a MV <80% of a given patient's predicted MV based on a body surface area formula. "Un-Safe" MV was considered to be <40% of Predicted MV sustained for at least 2 minutes.

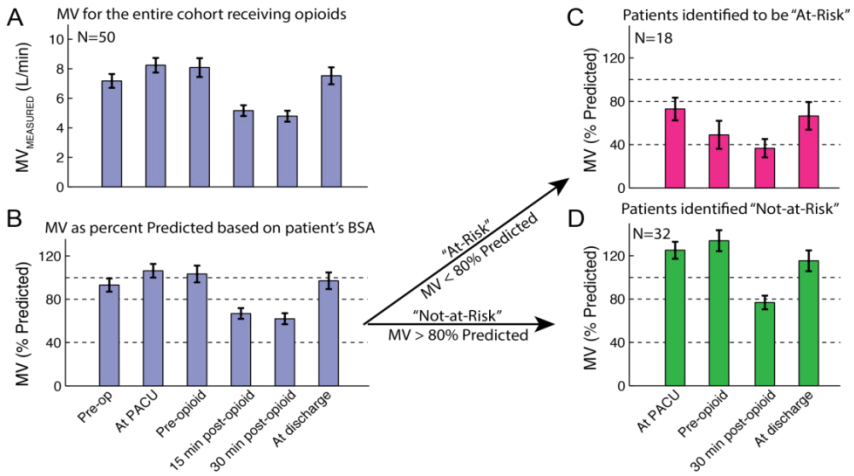


Figure 1: A) MV measurements at various time points in the PACU. Across the entire patient population a distinct depression in MV within 15 minutes of the first opioid dose in the PACU was seen. The average MV across the whole population did not noticeably decrease and recovers to baseline prior to discharge. **B) MV across the cohort calculated as percent predicted by BSA.** The plot demonstrates MV as Percent Predicted (MV_{PRED}), and allows normalization of the opioid response to account for patient size. **C) Patients designated "At-Risk"** The red bars show the course of the 18 of 50 (36%) of patients who received an opioid dose when their MV was below 80% MV_{PRED} became "Un-Safe". **D) Patients designated "Not-at-Risk"** Green bars show the course of the remaining 32/ 50 (64%) of patients who received opioids when their MV was above 80% MV_{PRED} and had minimal respiratory depression.

C. Train-of-Four Monitoring Background:

Train-of-Four (TOF) is used as an indicator of the depth of neuromuscular block and adequacy of reversal. A normal TOF = 1.0, meaning that there is no fade (no decrease in the amplitude of the fourth response, T4, compared to the first response, T1).[11]
With increasing levels of neuromuscular block, the TOF decreases from 1.0 to 0, at which point the degree of block correlates with 80-85% neuromuscular receptor occupancy. This degree of block is sufficient for non-intracavitary surgeries. For abdominal, thoracic, intracranial surgeries, and for robotic, laparoscopic and bariatric surgery, all 4 of the TOF responses need to be blocked, corresponding to 95-100% receptor blockade. While facilitating surgery, this extreme degree of block is very difficult to reverse with traditional anticholinesterase drugs like neostigmine. In the vast majority of patients, reversal with neostigmine from this deep block may require 90-120 minutes, markedly increasing the surgical duration. Additionally, up to 40% or ALL patients who receive intraoperative NMBAs have been shown to exhibit significant residual neuromuscular block (TOF<0.9), and 0.8% of

these patients will suffer a critical respiratory event (CRE), defined as significant oxygen desaturation, respiratory failure, need for airway support and manipulation, aspiration of gastric contents or need for tracheal re-intubation.[11] Obviously, elderly patients or those with pre-existing pulmonary disease, obese patients, patients with hypothermia, hypoventilation, hypercarbia, those receiving antibiotics that potentiate NMBA block, etc. are at increased risk of CREs. Sugammadex has been shown to effectively and completely reverse NMBAs, and its use avoids residual neuromuscular block.[12]

D. Rationale for Proposed Research:

Assessment and management of respiratory function following NMB has been complicated by the lack of a cohesive and continuous monitoring system to guide clinical decisions. In conjunction with quantitative TOF measurements, continuous, quantitative respiratory monitoring using the ExSpiron System will be particularly useful in detecting residual NMB leading to varying degrees of respiratory depression. Recent data have shown that stratification of patients based on the ExSpiron MV as % of predicted MV (MV_{PRED}), prior to opioid dosing has made it possible to identify patients who are at risk for further decreases in MV and opioid-induced respiratory depression. In the proposed trial, we use the ExSpiron to assess the respiratory effects of residual NMB and the effects of sugammadex reversal in decreasing the incidence of pulmonary complications (CREs).

2.3 Study Design	**Research Plan** A. Experimental Design: Randomized Controlled Blinded Trial B. Sample size and statistical analysis: (See Section 2.7 below) C. Subject Criteria: 1) Inclusion Criteria: Patients undergoing surgery with general anesthesia Patients scheduled to receieve rocuronium or vecuronium for neuromuscular blockade Patients weighing ≥ 80 pounds Non-intubated patients prior to surgery Patients who are able to give informed consent. 2) Exclusion criteria: Patients unable to give informed consent. Patients scheduled to receive nonsteroidal neuromuscular blocking agents (succinylcholine or benzylisoquinolinium) Patients scheduled to receive steroidal neuromuscular blocking agents other than rocuronium or vecuronium. Any patient whose condition will not allow for placement of the electrode PadSet. Patients whose tracheas were not extubated in OR or PACU. Pregnant women. Patients with known severe renal impairment (estimated creatinine clearance < 30 mL/min) as documented in the medical record. Patients with known hypersensitivity to sugammadex or any of its components. 3) Withdrawal/Termination Criteria: Participants may withdraw from the study at any time for any reason, Investigators may terminate the study if this is determined to be in the best interest of the subject.

D. Risk/Benefit Assessment:

Sugammadex. Sugammadex has been FDA approved for clinical use in the US and it has been used worldwide since 2008. We plan to administer the smallest dose of sugammadex recommended for shallow neuromuscular block (2 mg/kg of actual body weight), a dose that has not been reported to cause allergic or any other side effects. The use of sugammadex may lead to complete reversal of residual neuromuscular block, and avoidance of the respiratory complications (CREs) associated with incomplete reversal after neostigmine.

TOF Measurement. This involves delivery of small electrical impulses from a nerve stimulator via surface ECG electrodes to a peripheral nerve (usually the ulnar nerve at the wrist) and measuring the muscle contraction in the innervated muscle (usually the adductor pollicis muscle or the thumb. This testing is used routinely in many centers in awakening patients in the PACU, and it is not associated with any adverse effects or patient discomfort. In fact, routine monitoring has been advocated routinely for decades, as it both decreases the incidence of CREs and other postoperative complications and increases patient satisfaction.[11,12]

ExSpiron Respiratory Volume Monitoring (RVM). The RVM device has been FDA cleared and is currently in clinical use. It is considered a "non-significant risk device". The device requires the application of monitoring PadSets to the patient's skin similar to EKG electrodes and, as such, poses minimal risk. It is possible that the electrodes may irritate the skin. The presence of skin irritation will be monitored and treated appropriately, and further subject participation with cease if it is significant. Collected data up to that point will be used for the study, unless the subject requests otherwise. Direct physical harm is extremely unlikely. Any adverse events will be documented and forwarded to the IRB as per adverse event (AE) reporting requirements.

There is always a risk for breach of confidentiality despite best efforts.

Categories of Risk:

1) Physical Risk: Sugammadex administration may result in temporary changes in taste sensation (disgeusia); allergic reactions have been reported exceedingly rarely at the dose we plan to administer (2 mg/kg). Rare allergic reactions have been reported in patients receiving the highest dose indicated, 16 mg/kg, which is 8 times higher than the dose we plan to

administer.

Cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after administration. Clinicians and study team members will be instructed to monitor for hemodynamic changes and administer anticholinergic agents such as atropine if clinically significant bradycardia is observed.

Patients with pulmonary history should be monitored for a potential risk of developing bronchospasm immediately or a few minutes after administration of sugammadex.

Women who are sexually active and use hormonal contraceptives, will be instructed to use an additional non-hormonal method of contraception (Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm); Intrauterine device (IUD); Abstinence (no sex)) for 7 days following study drug administration.

TOF Monitoring – this type of monitoring is recommended in all patients receiving neuromuscular blocking agents, and is used routinely intraoperatively and postoperatively in the PACU (and in the ICU) to detect residual neuromuscular block. This type of monitoring has been shown to reduce the incidence of CREs.

The ExSpiron is a non-invasive and safe device cleared by the FDA for monitoring MV, TV and RR. Prior to study start, the device and its components will undergo a standard safety check by the institutional medical engineering department. There is a minimal risk of skin irritation from the electrode PadSets, the same as for EKG pads.

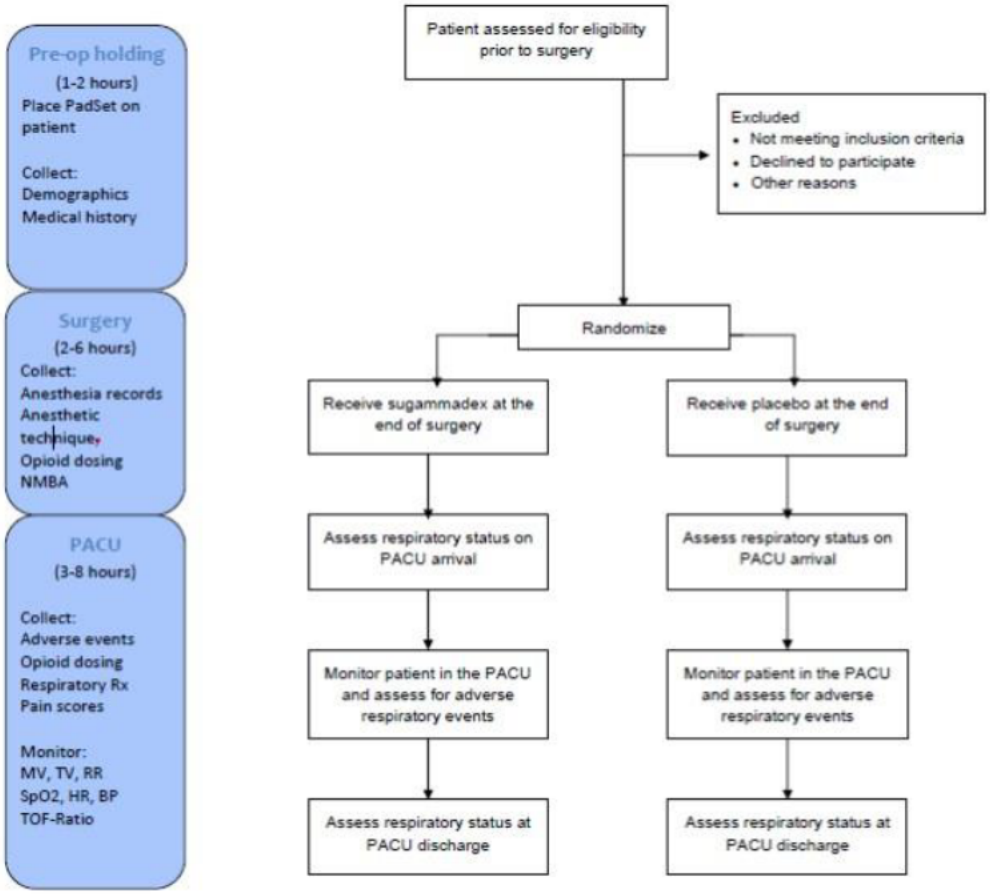
2) Psychological Risk: There is no known psychological risk to the participant. The study will be explained to them and they will be given the opportunity to ask questions. They will be informed that they can withdraw from the study at any time for any reason.

3) Social Risk: There is no known social risk to the patient. Participation in the study will not affect the subjects' ability to interact with family and friends post-operatively.

4) Economic Risk: There is no cost to the patient and their standard care will be unaffected.

<u>Benefit to Participating in the Study</u>: There are no direct benefits to subjects from participating in this research; however, information obtained from this study may benefit future patients.

2.4 Study Flowchart



2.5 Study Procedures

A. Specific Methods and Techniques used Throughout the Study:

300 patients undergoing surgical procedures requiring general anesthesia with mechanical ventilation will be recruited and consent will be obtained. The subjects will be randomized preoperatively to receive in the OR following the procedure and prior to extubation either sugammadex (Group 1, n=150 patients) or placebo (Group 2, n=150 patients). In all patients, intraoperative surgical and anesthetic management will follow the usual clinical routine at the two enrolling institutions. Once surgery is finished, emergence from anesthesia will occur as per usual clinical routine until the clinician determines that the patient is ready for tracheal extubation. Once the decision to extubate the trachea is made, the patient will receive intravenously either sugammadex 2 mg/kg or placebo in a blinded manner. The patient's trachea will be then extubated, and postoperative anesthetic care will proceed as per usual routine. Patients will then be transferred to the PACU for postoperative care and recovery. (This methodology will ensure that all 300 patients will receive at least the current standard of clinical care. Of the 300 patients, 50% of them (n=150 patients) may benefit from the administration of sugammadex,

which may decrease the incidence of residual neuromuscular block.)

1) The ExSpiron will be placed on the patients' chest prior to extubation. ExSpiron data will be collected starting prior to tracheal extubation, during transport from OR to PACU, and in PACU.
2) Patient care staff will be blinded to the ExSpiron numerical and trending data for MV, TV and RR, but the respiratory trace will be displayed to demonstrate that the ExSpiron is functioning. Of note, the gain on the trace is variable so the size of the breath visualized on the screen is not correlated to the volume of the breath. This will maintain blinding of the patient care staff.
3) TOF Monitoring with an objective monitor (TOF-Watch or StimPod) will be used in all patients once the decision to extubate the patients' trachea is made. The monitoring will continue in the PACU until full recovery (TOF=1.0) is documented. Monitoring will be performed as per usual clinical routine via surface ECG electrodes. In the PACU, the current amplitude will be decreased to 30-40 mA, current intensities that are used routinely for patient care in other centers and that do not result in patient discomfort.
4) Patient care staff will be blinded to TOF data. Only the investigator assigned to the PACU data retrieval will know the results of TOF Monitoring.
5) Patient care should follow standard hospital protocol.
6) Physiologic monitoring and clinical assessment data will be recorded as per standard protocol in the PACU.
7) All other therapies and medications including oxygen, CPAP, opioids and sedatives will be delivered in accordance with standard of care.
8) Doses and times of <u>all</u> medications (such as opioids, sedatives, etc.) or respiratory interventions (such as albuterol, respiratory treatment, suctioning, high flow oxygen, CPAP, BiPAP, etc.) will be recorded throughout the entire perioperative period (pre-op, OR, PACU).
9) Pain scores based on a standard analog scale (1-10) will be recorded. These will be obtained per standard clinical practice.
10) Arterial or venous blood gas values and Chest x-rays taken in the OR or PACU will be recorded when obtained as part of standard care.

B. Study Procedures

1) Screening and Recruitment:
Study personnel will review the surgery schedule to identify appropriate and eligible patients. Eligible

patients will be informed about the study and the study will be explained to them. They will be able to ask questions. If they would like to participate, written informed consent will be obtained. Recruitment at Mayo Clinic site will be conducted by Investigators on the day of surgery. Patients will be identified and approached before they are taken to the preoperative area. A private room located near the surgical area will be used for consenting of prospective participants. Family and/or friends will be allowed to remain with a patient during the consenting process. Patients usually arrive approximately 2 hours prior to their scheduled surgery time, which will be adequate time to discuss the study and allow patients to make an informed decision whether or not to participate in this research study.

2) Randomization:
   Patients will be randomized to one of two groups: administration of sugammadex (n=150) vs. placebo (n=150) prior to tracheal extubation in the OR.
3) Prior to Procedure (in the OR or preoperative area):
   i. For RVM monitoring, ExSpiron PadSet will be placed on the patient's thorax (see Appendix A for placement instructions). Deviations from standard placement will be documented. Once in the OR the ExSpiron will be connected and the ExSpiron will be synchronized to the ventilator.

   ii. For TOF monitoring, skin ECG electrodes will be placed along the ulnar nerve on the volar forearm, as per routine clinical protocol. Visual or tactile intraoperative monitoring of neuromuscular block level will be performed according to the clinicians' usual routine. At the end of surgery, once the clinician has determined that recovery of neuromuscular block is adequate (after administration of standard of care reversal agents) for maintenance of spontaneous ventilation, the TOF will be determined objectively (it will be measured with the currently available monitor, TOF-Watch or StimPod), and then the patient's trachea will be extubated, as per usual clinical routine. In 150 of the
   300 patients, a dose of sugammadex (2 mg/kg) will be administered, and then routine TOF measurements will be made in the PACU.
4) Operating Room (OR):
   a. Record all medications (dose, route, time)

b. Record surgery start and end times
c. Record position changes
d. Record intubation and extubation times

5) Recovery Room (PACU):
   a. Record PACU arrival and check device function.
   b. Record all medications (dose, route, time)
   c. Record form and dose of administered oxygen & all changes in administered oxygen or respiratory treatments of any kind
   d. Record PACU discharge time
   e. MV, TV & RR numerical data will be hidden and not

available for patient care decisions, but the continuous respiratory trace will be displayed. Patient care providers should not use this trace for clinical decision-making. If the trace is absent or grossly abnormal, this should be recorded and study staff notified to ensure proper device function.

f. TOF data will be hidden and not available for patient care decisions

6) Final Discharge Parameters: Record the patients' final discharge date and time (LOS) from the PACU.
7) De-identification: All study data will be de-identified and identifying information will be linked to a code only accessible to the study staff. The code will be destroyed following final data analysis.
8) Assessment of Subject Safety and Data Safety Monitoring Plan: All patients will be followed by one of the study investigators to ensure there are no complications associated with sugammadex administration (flushing, tachycardia, hypotension, etc). There are no expected complications of RVM monitoring. There are no expected complications associated with TOF monitoring, and in fact, such monitoring has been shown to improve patient safety by decreasing postoperative CREs and other complications.[11,12] External monitoring will not be provided; however, Principal Investigator will review all data for accuracy to ensure adherence to the approved protocol. Data will be recorded by the study coordinator and all electronic study-related files will be stored on a secured Mayo Clinic server. Drug accountability and dispension will be handled by pharmacy. Any potential adverse events will be assessed by the principal investigator for severity and relevance to the study drug.
9) Subject Participation:

a. Recruitment: Subjects will be recruited in the pre-procedure holding areas by the study team members prior to their surgery.

b. Screening Interview: Subject screening will be based on study personnel examining the surgery schedule of the next or same day to identify appropriate procedures scheduled and patient's eligibility.

c. Informed consent process and timing of obtaining of consent: Informed consent will be obtained by the study staff prior to surgery in the preoperative holding area, in patients requiring surgery and

general anesthesia and planned extubation in the OR. After a thorough review of the study. Sufficient time will be given to the patients, parents, guardians or legal representative to ask questions and decide on participation.

d. Location where study will be performed: University

of Texas, UTHealth at Houston and Mayo Clinic, Jacksonville, Florida operating holding areas, operating and recovery rooms, and intensive care units as applicable.

e. Personnel who will conduct the study include PI and research team members.

10) Subject fees: There are no fees for this study.

11) Procedures to protect subject confidentiality: A unique study ID number will be assigned to each subject as a means to de-identify the study data. A code will be kept separately with the PI. Study files will be kept in a locked office in a locked cabinet or a password-protected computer with encrypted study files. The location will be the PI office with restricted access. The code will be locked separately from study files in the PI office.

a. Certificate of Confidentiality: N/A

b. How data will be coded, recorded, and stored to protect confidentiality: All data will be de-identified. All data will be linked to the subject study ID by a code.

c. Data will be analyzed by institutional biostatisticians at UTHealth at Houston.

d. Parties who will have access to the data, including the key to the identity code: only Jaideep Mehta, MD and J. Ross Renew, MD and primary study staff will have access to the master study log/key. Other investigators and the clinical and engineering staff at Respiratory Motion, Inc. will only have access to de-identified data.

e. Parties who will have access to research records: Investigators on the study, Respiratory Motion, Inc. will have access only to de-identified records.

f. Collaboration: This study is performed in collaboration with Respiratory Motion, Inc.

g. Alternatives: The alternative to participating in this study is not participating.

h. How new information will be conveyed to the study subject and how it will be documented: Other than the initial explanation of the purpose and plan for the study, we don't expect new information to

	become available from the study that could affect a subject's willingness to participate. No new information of clinical relevance to the subject is expected from this study. Therefore no new information will be given to the patient. i. Payment: The participants will not be compensated for their participation in the study. j. Payment for a research-related injury: This is a minimal risk study. There are no plans to provide other compensation. If a participant is injured during this study, the study doctor will discuss the available medical treatment options with the subject. 12) Outcome: The primary outcome of this study is evaluation of the effects of sugammadex on the incidence of respiration complications postoperatively.
2.6 Study Duration	We anticipate that we will recruit the planned number of patients (n=300) at the two centers (UTHealth and Mayo Clinic) within 6 months of IRB approval and receipt of all necessary study materials and medications.

2.7 Statistical Analysis and Sample Size Justification	A. <u>Blinded Data Analysis:</u> The investigator will be responsible for overall analysis of the data with assistance from Respiratory Motion staff in analysis of RVM data. The study will be double blinded with no knowledge of drug vs. placebo administration by investigator, clinical care providers or researchers performing the primary data analysis. A patient can be unblinded on an urgent basis if it is deemed necessary for the clinical care of the patient. Study medication (sugammadex and placebo) will be prepared by the institutional pharmacy, and will be dispensed to the investigative team member according to the patient group assignment. The site study coordinator will call the pharmacy and alert them once a patient is enrolled in the study. The drug (sugammadex or placebo) will be prepared by the Pharmacy personnel according to the randomization sequence. The clinician administering the drug (sugammadex or placebo) will be blinded to the drug identity. The investigators will be responsible for analyzing the study data, and the analysts will be blinded to patients' group assignment during the execution of the study. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed and the investigators have been assured that the data are complete.

B. Statistical Analysis:

a. Using Fisher exact test, we will compare across the two groups the incidence of:

i. Sustained MV<80%MV_{PRED} for at least 1 minute in the first 15-30 minutes after arrival in PACU

ii. Sustained MV<40% MV_{PRED} for more than 10 contiguous minutes of the last 30 minutes prior to PACU discharge

iii.. Sustained MV<40%MV_{PRED} for at least 2 minutes after opioid administration (amongst patients receiving opioids in the PACU)

iv. Sustained MV<40%MV_{PRED} for at least 2 minutes in the absence of opioids (amongst patients w/o opioids in the PACU

v. Sustained MV<40%MV_{PRED} for at least 2 minutes after opioid administration (amongst patients receiving opioids in the PACU) when corrected for PACU LOS

vi. Sustained MV<40%MV_{PRED} for at least 2 minutes in the absence of opioids (amongst patients w/o opioids in the PACU when corrected for PACU LOS

vii. Adverse events, including:

1. Respiratory complications (O_2 desaturation, atelectasis, respiratory status requiring advanced monitoring, etc.)
2. Respiratory interventions (O_2 administration, CPAP, BiPAP, medications, etc.)
3. ICU or step-down unit transfer

viii. Normal TOF ratio (>0.90) at equivalent time points in the PACU (e.g. on arrival, at discharge, etc…)

b. Using 2-sample t-tests we will compare:

i. Average MV during the 15-30 minutes after arrival at the PACU

ii. Average MV during the 30 minutes prior to the time cleared for PACU discharge

iii. Average LOS in the PACU

iv. Average pain scores

v. Average total opioid dose (morphine equivalents) in the PACU

c. Using paired t-tests we will compare:
    i. MV, TV, and RR measurements before and after sugammadex administration
d. We will perform sensitivity and specificity analysis to evaluate the ability of sugammadex to:
    i. Decrease respiratory complications (O_2 desaturation, atelectasis, respiratory status requiring advanced monitoring, etc.)
    ii. Decrease the need for respiratory interventions (O_2 administration, CPAP, BiPAP, medications, etc.)
    iii. Decrease transfers to step-down or ICU
    iv. Decrease LOS in PACU
    v. Increase MV in the PACU at the following time points:
        1. On arrival
        2. After opioids
        3. At discharge
e. We will perform multi-factor Analysis of Variance (MFANOVA) with dependent variables: "sustained MV<40% MV_{PRED} for at least 2 minutes", "Adverse event", PACU LOS, etc… as defined in each hypothesis, based on demographics to demonstrate group uniformity.
f. We will use Pearson correlations and linear regressions, without regard to treatment group to compare:
    i. MV measurements and TOF ratios
    ii. MV measurements and total opioid dose
    iii. Pain scores and total opioid dose
    iv. MV measurements and pain scores

C. Multiplicity:

For the purposes of this work, we will treat Hypothesis A1 as a primary objective and A2 as a key secondary. We will consider $p<0.05$ to be statistically significant for the primary objective and this result will be the main outcome of our study. We will test the key secondary objective (at $p<0.05$ significance level) only if we have achieved significance with the primary.

We will continue with testing the remaining secondary hypotheses only if we have significant results from the primary and the key secondary. For each additional secondary hypothesis, we will calculate statistical significance both with and without Hochberg correction.[14] If we discover marginally significant effects in any of the remaining hypotheses, we will propose additional studies powered and geared towards specifically addressing said hypotheses.

D. Power/Sample Size:

Considering the study in general, the incidence of residual neuromuscular block in the PACU is estimated to be 35%.[11] Based upon a sample size of n=92 patients per group, this study has 80% power to detect a 5% difference between groups in incidence of residual block; this calculation is based on a standard deviation of 12%. We would need 100 patients per group in order to be conservative to observe this effect.However, more specific calculations related to our primary and key secondary hypotheses described below suggest we would need 150 patients per group to ensure we can adequately power these hypotheses.

(1) Low MV on arrival at the PACU. We will be comparing absolute measurements of MV as well as incidences of MV<80% across the two groups. Since comparisons of incidences usually requires more data, we are basing our sample size calculations on the incidence comparison.

Previous data suggest that as many as 33% of patients arrive in the PACU with MV<80% MV_{PRED}. We anticipate that in a group of similar patients receiving sugammadex at the end of surgery, the prevalence of MV<80%MV_{PRED} will decrease significantly, by approximately 18% ($\Delta p = 0.18$). To demonstrate this reduction with 80% power ($Z_\beta = 0.84$) at a $p < 0.05$ level ($Z_{\alpha/2} = 1.96$), the required sample size (assuming a large patient population) for each of the two groups (with and w/o sugammadex) can be calculated as follows:

$$n = \frac{2 \cdot \bar{p} \cdot (1 - \bar{p}) \cdot \left(Z_\beta + Z_{\alpha/2}\right)^2}{(\Delta p)^2} = 88.3$$

where $\bar{p} = \frac{p_1 + p_2}{2}$ is the average incidence in the two groups and $\Delta p = |p_1 - p_2|$ is the difference in the incidence of low MV across the two groups.

(2) Low MV at discharge from the PACU. Similarly with the PACU arrival, at PACU discharge we will compare both MV measurements as well as the incidence of Low MV and will calculate our sample size based on the incidence comparison

Previous data suggest that around 22% of patients leave the PACU

	with MV<40% MV_{PRED} and we anticipate that in a group of similar patients receiving sugammadex at the end of surgery, the prevalence of MV<40%MV_{PRED} will decrease in half by approximately 11% ($\Delta p = 0.11$). . To demonstrate this reduction with 80% power ($Z_\beta = 0.84$) at a p<0.05 level in a single-sided test ($Z_{\alpha/2} = 1.645$), the required sample size (assuming a large patient population) for each of the two groups (with and w/o sugammadex) can be calculated as follows: $$n = \frac{2 \cdot \bar{p} \cdot (1 - \bar{p}) \cdot \left(Z_\beta + Z_{\alpha/2}\right)^2}{(\Delta p)^2} = 143.2$$ where $\bar{p} = \frac{p_1 + p_2}{2}$ is the average incidence in the two groups and $\Delta p = \lvert p_1 - p_2 \rvert$ is the difference in the incidence of across the two groups. Hence , to adequately powere our key secondary hypothesis, we plan on recruiting 300 patients (150 in each group).
2.8 Specific Drug Supply Requirements	All drugs used in the course of providing medical care for the 300 patients will be supplied by the institutions participating in this protocol, with the exception of the investigated drug, sugammadex. A request will be made to the sponsoring company, Merck, to supply the sugammadex necessary for the 150 patients enrolled in the sugammadex study arm. Institutional pharmacies will be responsible for dispensing the test drugs (sugammadex and placebo) in a blinded fashion, based on the study group assignment. The test drugs (sugammadex and placebo) will be packaged and labeled by the institutional pharmacy in a blinded fashion.

2.9 Adverse Experience Reporting	1) Definition of Serious Adverse Event (SAE) and Adverse Event (AE): The PI and co-investigators will ensure that all patients have appropriate study consent and that protocols are followed. Data collection and device use pose minimal risk that cannot be further categorized. a. Reporting timeframe for serious adverse events (SAEs) and adverse events (AEs): Any adverse event will be reported by study personnel to the IRB per IRB standard protocol. Any SAE will be reported by the PI to the IRB within 24 hours along with a detailed report and enrollment will cease until the IRB has reviewed the event. b. Accountability procedures as they relate to drugs, devices, and data: Data to be collected will include device measurements of patient respiratory impedance values, during the procedure and after the procedure. Data regarding patient demographics, height, weight, any relevant pulmonary medical or surgical history and any complications will be obtained from the medical record. Data collected from each subject by the ExSpiron device will be stored under the subject's study ID. All other data collected will be stored electronically under the subjects study ID. Data collection sheets will be used to collect information regarding vital signs, medications and events. All information will be de-identified and protected in a secure office by either lock or key or password protection on a secure computer in the PI office. The code will be a paper folder kept under lock and key in a cabinet separate location from other study data files in the PI office. PI and co-investigators will be responsible for monitoring study data collection. The study will be stopped when we reach the endpoint of accruing data in 300 patients (150 in each arm) or if the Data Safety Monitor deems it necessary.

2.10 Itemized Study Budget	Please see attached budget worksheet.
2.11 References	**References:** 1. Aniskevich S, Leone BJ, Brull SJ. Sugammadex: a novel approach to reversal of neuromuscular blockade. Expert Rev Neurother 2011; 11:185–98. 2. Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium–induced blockade with sugammadex. Anesthesiology 2008;109:816–24. 3. Naguib M, Brull SJ: Update on neuromuscular pharmacology. *Curr Opin Anaesthesiol 2009; 22:483-490. PMID: 18384229* 4. Panasyuk A, Lalli M, Panasyuk S, Yocum N, Desmarais L, Lew R, Freeman J. Assessment of a continuous monitoring technique to measure adequacy of respiration. *Circulation.* 2011; 124: A13398. 5. Freeman J, Lalli M, Yocum N, Panasyuk A, Panasyuk S, Lew R. Non–Invasive monitoring of tidal volume and minute ventilation in non–intubated patients. *Crit Care Med*. 2011; 12: 88. doi: 10.1097/01.ccm.0000408627.24229.88. 6. Freeman J, Panasyuk A, Lalli M, Yocum N, Panasyuk S, Lew R. Assessment of a technique to continuously monitor respiratory status without patient cooperation. *Am. J. Respir. Crit. Care Med*. 185: A3788. 7. Freeman J, Yocum N, Panasyuk A, Lalli M, Panasyuk S, Fahy D, Messana E, Voscopoulos C. Evaluation of the accuracy of a continuous, non–invasive system for monitoring tidal volume, respiratory rate and minute ventilation in non–intubated patients. http://www.asaabstracts.com/strands/asaabstracts/abstractList.htm;jsessionid=410A076E96A999B5A9DE42F10145E0A1?index=8&year=2012. 8. Voscopoulos C, MacNabb CM, Brayanov J, Qin L, Freeman J, Mullen GJ, Ladd D, George E. The evaluation of a non–invasive respiratory volume monitor in surgical patients undergoing elective surgery with general anesthesia. J Clin Monit Comput. [epub ahead of print] July 2014; doi: 10.1007/s10877–014–9596–0.

	9. Voscopoulos C, Brayanov J. Ladd D, Lalli M, Panasyuk A, Freeman J. Evaluation of a novel non-invasive respiration monitor providing continuous measurement of minute ventilation in ambulatory subjects in a variety of clinical scenarios. *Anesth Analg.* 2013; 117: 91-100. 10. Voscopoulos C, MacNabb CM, Freeman J, Galvagno SM, Ladd D, George E. Continuous non-invasive respiratory volume monitoring for the identification of patients at risk for opioid induced respiratory depression and obstructive breathing patterns. *J Trauma Acute Surg.* 2014; 77: S208-S215. doi:10.1097/TA.0000000000000400. 11. Murphy GS, Brull SJ: Residual neuromuscular block: Lessons unlearned. Part I: Definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg* 2010; 111:120-128. PMID: 20442260 12. Brull SJ, Murphy GS: Residual neuromuscular block: Lessons Unlearned. Part II: Methods to reduce the risk of residual weakness. *Anesth Analg* 2010; 111:129-140. PMID: 20442261 13. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. Br J Anaesth 2007; 98:302-16 14. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika1988;75:800–2
2.12 Publication Plan	We plan to present the study results at one of the major international anesthesia meetings (ASA Annual Meeting, IARS Annual Meeting, NY PGA Meeting), followed by publication in Anesthesiology or Anesthesia & Analgesia journals. We anticipate there will be at least two abstracts (residual neuromuscular block and respiratory depression) and one full manuscript (combining the two outcomes).
2.13 Curriculum Vitae	J. Ross Renew, MD– CV attached. Jaideep Mehta, MD, MBA - CV attached
2.13 Protocol Submission for Investigator- Initiated	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com