Official title: Role of Sugammadex as Reversal Agent in Patients Extubated Immediately After Isolated Coronary Artery Bypass Grafting Surgery

NCT number: NCT03939923

Document date: 09/25/2020

Informed consent and Protocol Summary

More Than Minimal Risk Consent and HIPAA Form

Principal Investigator:	Matthew Ellison, MD
Department:	Anesthesiology
Protocol Number:	1806161309
Study Title:	Role of Sugammadex as Reversal Agent in Patients Extubated Immediately After Isolated Coronary Artery Bypass Grafting (CABG) Surgery MISP # 57655
Co-Investigators:	Anesthesiologists: Dr. Brian Grose, Dr. Heather Hayanga, Dr. Roy Henrickson, Dr. Jeff Puette, Dr. Hong Wang, Dr. Daniel Sloyer, Dr. Pavithra Ellison, Dr. Mir Ali Abbas Khan, Dr. John Bozek, Dr. Elizabeth Shaffer Cardiac surgeons: Dr. Chris C. Cook, Dr. Vinay Badhwar, Dr. Harold G. Roberts, Dr. Lawrence Wei CRNAs: Seth Hoblitzell, Deborah Street, Jennifer Szelong
Sponsor:	Investigator Initiated: Merck Investigator Studies Program (MISP) #57655

Contact Persons

In the event you experience any side effects or injury related to this research, you should contact Dr. Ellison at (304) 598-4122. (24 hour contact: (304) 598-4000 ext. 76263). If you have any questions, concerns, or complaints about this research, you can contact Dr. Ellison at (304) 598-4929.

For information regarding your rights as a research subject, to discuss problems, concerns, or suggestions related to the research, to obtain information or offer input about the research, contact the Office of Research Compliance at (304) 293-7073.

In addition, if you would like to discuss problems, concerns, have suggestions related to research, or would like to offer input about the research, contact the Office of Research Integrity and Compliance at 304-293-7073.

Introduction

You, _____, have been asked to participate in this research study, which has been explained to you by _____. This study is being conducted by Dr. Matthew Ellison in the Department of Anesthesiology at West Virginia University with funding support and Sugammadex (Bridion®) provided by Merck Investigator Studies Program.

Purpose of the Study

You are having surgery called Coronary Artery Bypass Grafting (CABG), which has been explained to you by your surgeon. Patients undergoing the CABG procedure will qualify for a research study if they meet the study requirements.

The main purpose for this study is to collect data on the use of muscle relaxants and 2 types of Food and Drug Administration (FDA) approved reversal agents; 1) Neostigmine, and 2) Sugammadex, to see if Sugammadex will reduce the time to removal of the breathing tube and improve other post-operative outcomes in patients with Coronary Artery Bypass Grafting (CABG).

WVU expects to enroll approximately 84 subjects. WVU is the only site enrolling subjects for this study.

Description of Procedures

This study involves collecting data.

You are eligible to participate in this study since you are going to have a CABG procedure, you are between the ages of 18 to 75, and you don't have an allergy to any of the medications that we may use as part of your anesthetic.

<u>Screening phase</u>:
You will discuss this consent with the research staff in the clinic or surgery suite. You may take a copy of this form home to read and make a decision prior to your procedure date.

Participation is voluntary and if you decide to participate please inform the staff who will go through the consent process with you.

<u>Treatment phase: Surgery</u>
There are two surgery groups; both groups will receive standard of care treatments. Standard of care is the standard medical care you receive regardless of if you participate in a study. The research team will collect data on the groups. You will be given a unique study ID number (i.e. 0001-ABC) to keep your information confidential. The Principal

Investigator and study staff will have access to the master code that links you to the study ID number. It will be stored on a computer and is password protected.

Both groups will receive a standard general anesthetic and all other standard medications given as part of a general anesthetic for CABG surgery.

Patients will have an equal chance of being randomized into 1 of 2 groups (like flipping a coin).

Group 1 will receive reversal of paralysis with a medication called neostigmine. (Standard of care)

Group 2 will receive reversal of paralysis with a medication called Sugammadex. (Standard of care)

Follow-up phase:
Cardiac Intensive Care Unit (CICU):

Data recorded for this study includes (current standard of care):

- Vital signs, i.e. blood pressure, heart rate and respirations, and oxygen levels while you are in the CICU or up to 2 hours of your CICU stay, if you stay longer.
- "Return of swallowing function" This is done before you are fed.
- You may receive a phone call within 30 days if you have had an adverse event such as pneumonia (infection in your lungs), palpitations, shortness of breath, low oxygen levels after procedure, re-intubation (replace tube in throat to help you breath). If you have not had an adverse event you will be finished with the study after discharge from the CICU.

Your participation may be terminated by the investigator without your consent at any time if the investigator feels it is necessary or for your safety.

Risks and Discomforts

Drugs often have side effects. The drugs used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of uncommon or previously unknown side effects. There may be reasonably foreseeable invasive or non-invasive risks or discomforts due to your surgery. You will discuss and sign a surgery consent with your surgeon and anesthesia consent with your physicians who take care of you.

Neostigmine Side effects
Serious side effects may include: muscle weakness, slurred speech, vision problems,

feeling like you might pass out, severe stomach cramps or diarrhea, trouble breathing, cough with mucus, fast or slow heart rate, convulsions.
Less serious side effects may include: headache, drowsiness, mild nausea, vomiting, gas, urinating more than usual, cold sweat, warmth or tingly feeling, mild rash or itching.

Sugammadex (Bridion®) Side effects
Most common side effects seen in >10% of subjects are vomiting, pain, nausea, and headache. Some serious side effects may include slow heart rate, low blood pressure and allergy to the medication.

This study may involve risks to the unborn child. For this reason, women who are pregnant may not participate.

If you are a woman who is able to become pregnant, you must use a medically approved method of birth control while you are on this study and 7 days after receiving Sugammadex.

Men who are able to father a child should never have unprotected sex with a woman while on this study because it is not known if the drug is present in semen or sperm.

Alternatives

You do not have to participate in this study.

Benefits

Possible benefits that may result from your participation include the improvement of your health, but since it is not known whether either therapy will be effective in your case, you may not receive any benefit or your condition may worsen. The knowledge gained from this study may eventually benefit others.

Financial Considerations

If you are randomized to Group 2, Sugammadex (Bridion®) will be provided by the Merck Investigator Studies Program at no cost to you.

There are no special fees for participating in this study, but any expense associated with current therapy or treatment of side effects will be billed to you or to your insurance company. You may wish to consult your insurance carrier prior to entering this study.

Voluntary Compensation

If you are injured as a result of this research, treatment will be available. Responsibility for this treatment will be borne by you or your insurance company. In the event that you are physically injured as a result of participating in this research, care will be available. You will, however, be responsible for the charges for the care. There is no commitment to provide any compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact the investigator, Dr. Ellison at 304-598-4929 if you are injured or for further information.

Confidentiality

Any information about you that is obtained as a result of your participation in this research will be kept as confidential as legally possible. Your research records and test results, just like hospital records, may be subpoenaed by court order or may be inspected by the study sponsor or federal regulatory authorities (including the FDA) without your additional consent.

In addition, there are certain instances where the researcher is legally required to give information to the appropriate authorities. These would include mandatory reporting of infectious diseases and mandatory reporting of information about behavior that is imminently dangerous.

In any publications that result from this research, neither your name nor any information from which you might be identified will be published without your consent.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

HIPAA

We know that information about you and your health is private. We are dedicated to protecting the privacy of that information. Because of this promise, we must get your written authorization (permission) before we may use or disclose your protected health information or share it with others for research purposes.

You can decide to sign or not to sign this authorization section. However, if you choose not to sign this authorization, you will not be able to take part in the research study. Whatever choice you make about this research study will not have an effect on your access to medical care.

Persons/Organizations Providing the Information

Patient/West Virginia University Hospitals

Persons/Organizations Receiving the Information

- The research site carrying out this study. This includes UHA and UHA affiliated entities, WVU, WVU Hospitals, WVU Medicine, and West Virginia United Health System. It also includes the site's research staff and medical staff.
- Health care providers who provide services to you as part of this research study.
- Laboratories and other people and groups that look into your health information as part of this study in agreement with the study protocol.
- The United State Department of Health and Human Services (which includes the National Institutes of Health (NIH), Food and Drug Administration (FDA)) and other groups that have the right to use the information as required by law.
- Merck and the people and companies that they use to oversee, manage, or conduct the research.
- The members and staff of any Institutional Review Board (IRB) that oversees this research study.
- West Virginia University Office of Research Compliance and Office of Sponsored Programs.

The Following Information Will Be Used

Information from your existing medical records and new information about you that is created or collected during the study such as: history and physicals, operative reports, inpatient notes, clinic visit notes, nursing and staff notes, laboratory results, x- rays, EKG results, demographic data, pulmonary tests, imaging scans and study forms.

The Information is Being Disclosed for the Following Reasons

- Review of your data for quality assurance purposes
- Publication of study results (without identifying you)

You May Cancel this Authorization at Any Time by Writing to the Principal Investigator

Matthew Ellison, MD at 1 Medical Center Drive Department of Anesthesiology P. O. Box 8255 Morgantown, WV 26506

If you cancel this authorization, any information that was collected already for this study cannot be withdrawn. Once information is disclosed, according to this authorization, the recipient may disclose it and then the information may no longer be protected by federal regulations.

You have a right to see and make copies of your medical records. You will not be able

to see or copy your records related to the study until the sponsor has completed all work related to the study. At that time you may ask to see the study doctor's files related to your participation in the study and have the study doctor correct any information about you that is wrong.

This authorization will expire at the end of the study unless you cancel it before that time.

Voluntary Participation

Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time.

Refusal to participate or withdrawal will not cause any penalty or loss of benefit to which you are otherwise entitled. The PI will discuss the risks and benefits of withdrawal with you. Refusal to participate or withdrawal will not affect your current or future care, or your employee status at West Virginia University (if applicable).

In the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether or not to continue your participation.

You have been given the opportunity to ask questions about the research, and all of your questions have been answered to your satisfaction.

Upon signing this form, you will receive a copy.

I willingly consent to participate in this research.

Signatures

Date	Subject Signature	Printed Name

The participant has had the opportunity to have questions addressed. The participant willingly agrees to be in the study.

Date	Investigator Signature	Printed Name

Requirements for Submitting a Full Proposal	
Section #1 - MISP Protocol Identification	
Study Title:	**Role of Sugammadex as Reversal Agent in Patients Extubated Immediately After Isolated Coronary Artery Bypass Grafting (CABG) Surgery Amendment 2 Date: 17Oct2019**
Request Date:	**Feb 23, 2018**
Institution Name	**West Virginia University**
Investigator Contact Information: – Full address – Phone No. – Fax No. – e-mail address	**Matthew Ellison, MD** **1 Medical Center Drive P.O. Box 8255** **Morgantown, WV 26506** **office (304) 598-4929** **coordinator: (304) 598-6193** **Fax (304) 285-1917** **mellison@wvumedicine.org**

Section #2 - Core Protocol	
2.1 Objectives & Hypotheses	**2.1 List the objectives.** The purpose of this study is to examine whether the use of Sugammadex will reduce time from reversal to extubation and improve other post extubation outcomes in Coronary artery bypass grafting (CABG) patients. **2.1.1 List the clinical hypotheses.** **Primary Hypothesis: Use of muscle relaxant and reversal with Sugammadex at the end of CABG procedures will shorten the time to extubation after reversal at the end of the procedure (procedure stop time) as compared to reversal using neostigmine and glycopyrrolate.** **Secondary Hypotheses:** The group of subjects who receive sugammadex at the end of CABG procedures as compared to Neostigmine and glycopyrrolate group will have ➢ Improved stability in vital signs post-reversal (less variability in both Heart rate and blood pressure) ➢ Improved lung function at post-extubation and measured at 30-60 minutes post extubation (higher FEV1, FVC,FEV1/FVC ration and peak expiratory flow using Micro I spirometry) ➢ Improved return of swallowing function measured at 30-60 minutes following extubation (Nursing aspiration screening tool) Other exploratory measures are that subjects in the Sugammadex group as compared to Neostigmine and glycopyrrolate group will have: ➢ Less reintubation the first 24 hours ➢ Decreased length of ICU stay ➢ Decreased rate of postoperative pneumonia during the perioperative period (hospital stay) ➢ Decrease rate of postoperative cardiac arrhythmias in the first 2 hours after the procedure.

2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Enhanced recovery pathways and early extubation of subjects undergoing cardiac procedures has now become mainstay, especially with the advent of minimally invasive procedures (1-2). To facilitate optimal recovery after extubation; muscle strength is vital to prevent reintubation, improved deglutition and quicker transition to lower O2 requirements, and better respiratory and cardiac hemodynamics (2). It also expedites de-escalation of acuity of care. Several studies have shown residual muscle weakness after full reversal with neostigmine and glycopyrrolate (5-7). Sugammadex is a direct reversal agent and can provide superior muscle strength, which optimizes respiratory function thereby preventing atelectasis, hypoxia and potentially avoiding reintubation (8-13). Prolonged intubation rates at WVU hospital Jan 2016-Jan 2017 is 4% for >24 hours and 4.5% for re-intubation within 24 hours after CABG. The number of patients at WVU that are unanticipatedly left intubated after CABG is not available at this time as consistent documentation of plan to extubate at beginning of case is not done. The exclusion criteria will hopefully minimize "High risk" subjects that maybe enrolled in the study. Surgical issues, bleeding etc. are unanticipated events but may have an even distribution in both groups. The most impact we would like to see in this study is to ask the question on subjects that we would normally extubate after isolated CABG – do they do better with Sugammadex or Neostigmine? Right-censoring with respect to death seems to be a valid consideration here. The Kaplan-Meier method takes this into account. More than right censoring- we may be partially truncating the results by restricting the age and stringent exclusion criteria. This will allow us to see the effect on the group of subjects for which it is intended.
2.3 Study Design	This study is a prospective, clinical interventional, randomized single-blinded single-center design. The nurses in the CVICU will be blinded to treatment allocation (Group 1 or 2). After IRB approval, subjects will be consented in the clinic by the PI or CO-I for the study. After written consent is obtained and a copy provided to the subject, the following inclusion and exclusion criteria will be reviewed. The subject must meet all inclusion criteria and no exclusion criteria to qualify for the treatment phase. Any subject that does not qualify will not be included in this study. **Inclusion Criteria:**

- Age 18 – 75 years
- ASA physical status I-4
- Isolated CABG surgery
- Ability to give written informed consent

Exclusion Criteria:

- Any other surgical procedure concomitant to CABG surgery
- Known or suspected neuromuscular disease/pre-existing weakness
- Creatinine clearance less than 30 ml/min
- Bradycardia of less than 40 beats/min
- Pregnancy, breastfeeding women
- Known or suspected allergy to BRIDION® (sugammadex), neostigmine, or rocuronium
- Patients with contraindications towards sugammadex, neostigmine, or rocuronium
- Patients included in another trial within the last 30 days
- Patients with legal guardians or surrogate decision-making
- Female Patients who refuse to use non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days if receiving sugammadex.(14)
- Patients undergoing emergency surgery
- Patient refusal
- Patients with EF<30%
- Patients with severe restrictive and/or obstructive lung disease requiring supplemental oxygen therapy
- Patients with OSA with documented apnea hypopnea index (AHI) of >15 or moderate sleep apnea
- Patients with BMI greater than 40

Randomization: Subjects will be randomized, using a block randomization scheme, to one of the two anesthetic groups. The block randomization scheme will use random block sizes varying from 2 to 6 patients per block. Subjects will receive a unique study id number (i.e., subject 1 = 0001-{3 initial, i.e. A-B-C}). The randomization scheme will be developed by the statistician. The master list of study IDs and reversal treatment allocations will be held by the PI and research coordinator. Strict adherence to the sequence of treatment allocations will be maintained.

Group 1: Intubation with rocuronium at 1.0-1.2 mg/kg (vitals maintained within 20% of baseline). Subjects may be re-dosed with rocuronium at 0.1-0.4 mg/kg during the procedure to maintain 1-2 twitches on Train of Four (TOF) monitor reading recorded every 15 minutes.

Group 1 (control) will receive reversal with neostigmine (0.07mg/kg up to 5 mg maximal dosage) and glycopyrrolate (00.007- up to 0.70 mg maximal dosage).

Group 2: Intubation with rocuronium at 1.0-1.2 mg/kg (vitals maintained within 20% of baseline). Subjects may be re-dosed with rocuronium at 0.1-0.4 mg/kg during the procedure to maintain 1-2 twitches on TOF watch monitor reading recorded every 15 minutes. Group 2 (treatment) will receive reversal with Sugammadex (2mg/kg).

At induction and emergence TOF monitor reading will be recorded every 5 minutes

At the EMR documentation of "procedure stop", patients will receive the reversal agent/s.

Extubation will occur when the subject meets the following criteria:

Temperature of at least 35.5 degrees centigrade
Rapid Shallow Breathing Index less than 105
Tidal volume : >5 cc /kg
Respiratory rate: >8 /min
O2 saturation > 95% ON 100% inspired oxygen
Following verbal commands

Outcome Measures

Primary outcome

Time to extubation:

West Virginia University Hospitals use an electronic medical record (EMR) to chart "procedure stop." The definition for "time to extubation" is from the time we chart "procedure stop" to the time of "extubation".

Secondary outcomes

1. Heart rate and blood pressure post-reversal prior to extubation
2. Tidal volume post-reversal prior to extubation
3. RESPIRATORY PARAMETERS-(higher FEV1, FCV, FEV1/FVC ratio, peak expiratory flow) – measured by 3 repeated measurements with micro I spirometry between30-60 minutes post extubation
4. Nursing Aspiration Screening Tool administered between 30 – 60 mins post extubation.

Other Exploratory outcomes:

5. O2 saturation post-extubation for subsequent 2 hours documented every 15 minutes
6. Post-extubation FiO2 requirements in subsequent 2 hours
7. Length of stay in the ICU
8. Reintubation incidence in the first 24 hours
9. Postoperative respiratory complications, i.e. pneumonia during perioperative hospital stay
10. Postoperative cardiac complications, i.e. arrhythmias in the first 2 hours.

Nursing Aspiration Screening Tool:
Part A:
Patient awake and alert, is able to be positioned, can cough when asked, able to follow command to lick top and bottom lip, is able to breathe freely.
Part B:
A teaspoon is used to place distilled water on each subject's tongue, 3 mL each time 2 consecutive times. Then 3 ounces of water intake. The patients are asked to swallow the water to evaluate the swallowing ability. Aspiration of fluid (choking) subjectively divided into 4 categories: normal, no choking or hoarse voice after swallowing; mild, no choking but slight hoarseness of voice; moderate, no choking but a clearly identifiable hoarseness of voice; severe, choking.

Independent Data and Safety Committee Monitoring: Data and safety monitoring is a requirement of our institutional IRB (WVU IRB) and is standard for all clinical studies. Independent Data and Safety Monitoring Committee will be comprised of individuals not involved with the study who will review the data and make recommendations to continue or stop the study to the Principal Investigator.

Following the WVU IRB Independent Data and Safety Monitoring Plan, a quality assurance audit will be performed by the IDSMC when 20% of the patients (*n*=84) have been recruited. This audit will include, but not be limited to, the review of informed consent process, eligibility confirmation, adherence to protocol procedures and treatment plans, pharmacy records and storage, and regulatory documentation. Adverse events and severe adverse events such as pneumonia, arrhythmia, and reintubation within 24 hours will be compared in both groups.

Data integrity and protection: Data will be recorded and kept in a password protected file in the coordinators office. PI will not be reviewing the data for individual cases. PI will ensure that data is entered appropriately by the research staff.
An independent data analysis team – comprised of someone well versed in statistics, research pharmacist and 2 physicians not involved in the study but knowledgeable in subject protection and safety will perform an independent review after first 20 subjects.
Communication to the PI will only consist of determinations and not result.
(i.e. approval to continue the study or to stop the study)
No analysis related to or involving the primary outcome is required or will be performed at this time.

The pharmacist being the only person with access to the random assignment list and labeling the treatments A and B, with un-labelling happening only after all the data has been collected. The Study coordinator will be maintaining the data sheet (not the PI) and that this will not be available to the PI throughout the course of the study.

Adverse Event Assessment: Defined as any unfavorable and unintended medical occurrence, symptom, or disease temporally associated with the use of a medical treatment of the subjects whether it is associated or related to the medical treatment. The Principal Investigator will identify and make adverse events assessments. Adverse events and severe adverse events such as pneumonia, arrhythmia, and reintubation within 24 hours will be compared in both groups.

Subject Total: 84 completed

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This website will not include information that can identify subjects. At most, the website will include a summary of the results.

2.4 Study Flowchart

Timetable of Investigation (after contract signed & IRB approval):

	Year 1 Sep 2018 – Sep 2019				Year 2 Oct 2019-Oct 2020
	Q1	Q2	Q3	Q4	
IRB Approval/ Renewal					
Subject Screening/ Enrollment					
Data Collection					
Statistical Analysis					
Writing/ Presentation					

2.5 Study Procedures

Screening & Consent: After IRB approval, subjects will be recruited in the clinic and screened for study eligibility. The following inclusion and exclusion criteria will be reviewed. The subject must meet all inclusion criteria and no exclusion criteria to qualify for the treatment phase. Patients who are eligible and interested in participating will be consented by the Principal Investigator or co-investigator for the study.

Inclusion Criteria:

- Age 18 – 75 years
- ASA physical status I-4
- Isolated CABG surgery
- Ability to give written informed consent in English

Exclusion Criteria:

- Any surgical procedure concomitant to CABG surgery
- Known or suspected neuromuscular disease/pre-existing weakness
- Creatinine clearance less than 30ml/min
- Bradycardia of less than 40 beats/min

	➢ Pregnancy, breastfeeding women ➢ Known or suspected allergy to BRIDION® (sugammadex), neostigmine, or rocuronium ➢ Patients with contraindications towards sugammadex, neostigmine, or rocuronium ➢ Subjects included in another trial within the last 30 days ➢ Patients with legal guardians or surrogate decision-making ➢ Female subjects that refuse to use non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days if receiving sugammadex (14) ➢ Patients undergoing emergency surgery ➢ Patient refusal ➢ Patients with EF<30% ➢ Patients with severe restrictive and/or obstructive lung disease requiring supplemental oxygen therapy ➢ Patients with OSA with documented (apnea hypopena index (AHI) >15 or moderate sleep apnea ➢ Patients with BMI greater than 40 **<u>Treatment Phase</u>** **Surgery:** Subjects will receive a unique study ID number (i.e., subject 1 = 0001-{3 initial, i.e. A-B-C}) if surgery is performed. Patients will be randomized, using a block randomization scheme, to one of the two groups, as outlined in the Study Design section. Strict adherence to the sequence of treatment allocations will be maintained. Group 1 (control) will receive reversal with neostigmine (0.4-0.07 mg/kg mg/kg up to 5 mg maximal dosage) and glycopyrrolate (0.007-up to 0.7 mg maximal dosage). Group 2 (treatment) will receive reversal with sugammadex 2 mg/kg. **Follow-Up:** Vital signs (i.e. B/P, HR, Respirations), oxygen saturations, Fio2 will be followed every minute in the OR from “procedure stop” and every 15 minutes post “procedure stop” for 2 hours in Cardiac Intensive Care Unit, (CICU), length of stay. CICU length of stay will be recorded. The reintubation incidence within 24 hours will be recorded. Adverse events and serious adverse events such as pneumonia, arrhythmia, and reintubation will be followed until resolution or 30 days post-treatment by phone call from research coordinator. **Subject Total**: 84 completed
2.6 Study Duration	The estimated time for subject enrollment is 12 months with publication and presentation of data following completion of data analysis.

2.7 Statistical Analysis and Sample Size Justification	**Power/Sample Size** All patients have a clearly defined time at which extubation begins and ends (See Section 2.3, Study Design). There will be no patients with unobserved end points (e.g. no loss to follow-up, attrition, or right censoring). Additionally, the Data and Safety Monitoring does not require the analysis of the primary research question prior to the completion of the study (See Section 2.3, Study Design, Independent Data and Safety Committee Monitoring subsection). Based on these considerations, powering for the primary outcome of extubation time used the log-rank test, Schoenfeld's method, and balanced allocation of patients to each group.(16-17) With minimum power of 80%, an alpha-level of 0.05, and an effect size of 0.542, a total of 84 patients are required with 42 patients per group. The effect size was derived using the median times-to-extubation to estimate the hazard ratio. An estimate of the median extubation time for neostigmine was taken as 19.0 minutes, a conservative estimate from the last two cohorts reviewing anesthetic management with robotic mitral valve repair, the closest analogous procedure for this study.(18) A 10 minute reversal time for neostigmine is taken as the minimum time for reversal.(17) Assuming analogous times between reversal and extubation, the total extubation time for sugammadex is estimated to be 10.3 minutes, 1.3 minutes for reversal with 9.0 minutes between reversal and extubation.(14) This minimizes the differential between neostigmine and sugammadex reversal (estimated minimum differential = 8.7 min). The anticipated minimal differential has positive clinical and financial ramifications (See Section 2.3 Study Design). **Statistical Analysis** We will use univariate statistics (e.g. mean, median, standard deviation, interquartile range) to summarize the collected data. Balance between the two groups for key patient variables (see Section 2.1 for examples) will be assessed using a two-sided two-sample t-test using unequal variances and the Welch modification to the degrees of freedom. For categorical variables, the Chi-square test will be used. If non-parametric tests or exact methods are required, we will use the Mann-Whitney U test and the Fisher-Freeman-Halton exact test respectively. The primary comparison of extubation time between the two groups will be assessed using the Kaplan-Meier method and log-rank test. Statistical significance will be assessed using a two-sided test with an alpha-level of 0.05. All statistical analysis will be performed using the R software environment for statistical computing and graphics. (20)

We assume that by randomization the number of subjects that may expire intubated will be equally distributed in both groups. **Moderately unequal censoring rates have a minimal effect on the power of tests used in analysis.** ***(****Beltangady, Mohan S., and Ralph F. Frankowski. "Effect of unequal censoring on the size and power of the logrank and Wilcoxon types of tests for survival data." Statistics in medicine 8.8 (1989): 937-945.****)***

Effect analysis for secondary outcomes

The study will have n = 84 subjects with equal allocation of controls and experimental subjects. The sample size was determined for the primary outcome with a power of 80% and significance level of 0.05.
Secondary outcomes will be analyzed as continuous variables in the data analysis.
A two-sample t-test and/or linear model will be used in the data analysis. Issues of multiplicity of tests will be examined before valid conclusions can be drawn. We will adjust for multiple comparisons using appropriate methods such as a Bonferroni correction or the Benjamini-Hochberg procedure (1995). (21,22)

A standard deviation of 0.65 correlates with approximately a 20% difference in the two groups which is usually clinically significant. **According to the widely-used scale established by Cohen, the effect size of 0.65 standard deviations, a statistic referred to as Cohen's *d*, falls between medium and large, and is generally expected to yield results that are practically relevant.** ***(****Cohen, Jacob. "Statistical power analysis for the behavioral sciences. 2nd." (1988): 25-27.****)***

Secondary outcomes analyzed:

1. Heart rate and blood pressure post-reversal prior to extubation

sample size of 42 subjects per group will have 80% statistical power to detect 0.65 standard deviations of mean difference between two treatment groups (i.e., an effect size of 0.65), using a two-sided two-sample t-test at a significance level of 0.05 with the power analysis software PS (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).

2. Tidal volume post-reversal prior to extubation

sample size of 42 subjects per group will have 80% statistical power to detect 0.65 standard deviations of mean difference between two treatment groups (i.e., an effect size of 0.65), using a two-sided two-sample t-test at a significance level of 0.05 with the power analysis software PS (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).

	11. RESPIRATORY PARAMETERS-(higher FEV1, FCV, FEV1/FVC ratio, peak expiratory flow) – measured by 3 repeated measurements with micro I spirometry between30-60 minutes post extubation. 3. sample size of 42 subjects per group will have 80% statistical power to detect 0.65 standard deviations of mean difference between two treatment groups (i.e., an effect size of 0.65), using a two-sided two-sample t-test at a significance level of 0.05 with the power analysis software PS (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). 4. Swallowing capacity measured by Nursing Aspiration Screening Tool administered between 30-60 minutes post extubation. sample size of 42 subjects per group will have 80% statistical power to detect 0.65 standard deviations of mean difference between two treatment groups (i.e., an effect size of 0.65), using a two-sided two-sample t-test at a significance level of 0.05 with the power analysis software PS (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).
2.8 Specific Drug Supply Requirements	**Phase 4 Study:** Drug – BRIDION®, sugammadex, will be supplied by Merck. Budget includes cost of inpatient pharmacist to receive drug from Merck, dispense drug, keep research accountability, and keep allocation blinded for the research study ($120/subject).
2.9 Adverse Experience Reporting	**Phase 4 Study:** FDA policy on reporting Form 3500
2.10 Itemized Study Budget	Please see attached budget
2.11 References	1. Badhwar V, Esper S, Brooks M, Mulukutla S, Hardison R, Mallios D, Chu D, Wei L, Subramaniam K. Extubating in the operating room after adult cardiac surgery safely improves outcomes and lowers costs. J Thorac Cardiovasc Surg. 2014 Dec;148(6):3101-3109. 2. Subramaniam K, DeAndrade DS, Mandell DR, Althouse AD, Manmohan R, Esper SA, Varga JM, Badhwar V. Predictors of operating room extubation in adult cardiac surgery. J Thorac Cardiovasc Surg. 2017 Jun 13. [Epub ahead of print]

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the reversal of muscle relaxation in general anaesthesia: a systematic review and economic assessment. Health Technol Assess. 2010 Jul;14(39):1-211.
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2.12 Publication Plan	Publications will be prepared for the Anesthesiology Journal and presentations will be prepared for the ASA meetings in fall 2020.
2.13 Curriculum Vitae	Please see attached in vision tracker
2.13 Protocol Submission for Investigator-Initiated Studies	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com Non-U.S. protocols should be submitted to the MSD office by the investigators.