Official Title:

A prospective digital quality improvement project to apply best clinical practices to patients at high risk of respiratory complications

NCT Number:

NCT04263363

Document Date:

3-4-2021

A prospective digital quality improvement project to apply best clinical practices to patients at high risk of respiratory complications

Sponsor: Merck & Co., Inc.

National Coordinating Investigator: Dr. Eilon Gabel, MD

Study Drug: Sugammadex

Protocol Number:

Study Sites: UCLA Ronald Reagan Hospital, University of California Los Angeles, UCLA Santa Monica Hospital

Lead IRB: UCLA Office of Human Research Protection Program
10889 Wilshire Blvd, Suite 830
Los Angeles, CA 90095-1406

National Clinical Trial (NCT) Identified Number **NCT04263363**

National Coordinating Investigator	Signature	Date
Dr. Eilon Gabel, MD		
Sponsor	**Signature**	**Date**

1.0 STATEMENT OF COMPLIANCE

This document is a clinical investigational plan for a human research study Sponsored by Merck Corporation. The study will be conducted in compliance with all stipulations of this protocol, ethical principles that have their origin in the

Declaration of Helsinki, the conditions of IRB/EC approval, applicable federal and local regulatory requirements, ISO-14155 and International Conference on Harmonization (ICH) E6 on Good Clinical Practice (GCP) guidance.

2.0 TABLE OF ABBREVIATIONS

Abbreviation	Meaning
OSA	Obstructive sleep apnea
GFR	Glomerular filtration rate
FDA	Food and Drug Administration
IRB	Institutional Review Board
PACU	Post Anesthesia Care Unit
AE	Adverse Event
SAE	Severe Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
Hb	Hemoglobin
RRUMC	Ronald Reagan UCLA Medical Center
EMR	Electronic medical record
BMI	Body mass index

3.0 PROTOCOL SUMMARY

Sponsor	Merck & Co., Inc.
Protocol Title	A prospective digital quality improvement project to apply best clinical practices to patients at high risk of respiratory complications
Drugs	The following FDA cleared drugs will be used in this study: • Sugammadex
Study Objectives	**Primary Objective** 1) Time to "fitness for discharge" from the recovery room, as noted by the time the anesthesiologist places the discharge order, before and after intervention.

	2) Incidence of hypoxemia in the PACU before and after intervention as defined by documentation oxygen saturation below 90% **Secondary Objectives** 1) Performance of identified best practices before and after intervention. 2) Incidence of hypoxemia in the PACU before and after intervention as defined by documentation of oxygen saturation below 95% 3) The duration of supplemental oxygen needed by high risk patients before and after intervention 4) Postoperative reintubation rate 5) Unplanned upgrade of care (defined as patients who are sent to the ICU after being admitted to a regular ward)
Study Design	Historical prospective comparative effectiveness trial
Study Phases	**Retrospective Data Analysis** Perform a retrospective analysis on data contained in our data warehouse on the incidence of respiratory dysfunction in the post-operative care unit (PACU) before and after the introduction of sugammadex into clinical practice. **Respiratory depression pathway implementation** Develop and implement a clinical best practice pathway designed to prevent postoperative respiratory complications in higher risk patients (such as those with OSA or preexisting respiratory disease) using education and clinical decision support in patients.
Sample Size	~13,000 retrospective and ~6,500 prospective
Clinical Sites	Ronald Reagan UCLA Medical Center, UCLA Santa Monica Hospital
Study Population	RRUMC or UCLA Santa Monica patients aged 18 and older who had a general anesthetic with either rocuronium or vecuronium.
Inclusion Criteria	One or more: • Obstructive or restrictive lung disease in EMR • OSA • Preoperative O2 sat <95% (avg/median of 12 hours before surgery) • BMI > 40 • Acute respiratory infection within 1 month prior to surgery

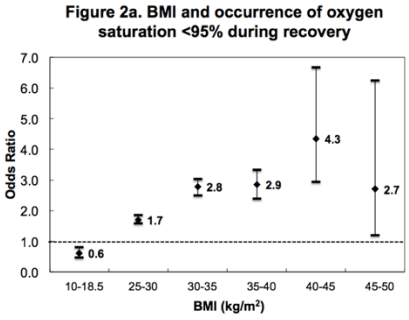
	• Previous history of airway pathology Two or more: • BMI>35 • Multiple intubation attempts • Surgical duration >2 hours • Upper abdominal surgery, intrathoracic surgery, or airway/head and neck surgery • Most recent Hb (within 6 months only) <10
Exclusion Criteria	• Pregnant or lactating (or gave birth within last year) • Age<18 • Documentation of allergy or previous reaction to sugammadex • GFR<30 • Neuromuscular disease (ICD codes) • Remain intubated/tach post-op • Surgery at a site other than RR OR or SM OR
Study Endpoints	1) PACU Discharge Time (primary endpoint) 2) Incidence of oxygen saturation <90 3) Incidence of oxygen saturation <95% 4) Duration of supplemental oxygen use in PACU 5) Reintubation rate 6) Unplanned Upgrade of Care
Safety Evaluation	All adverse events reported by participating clinicians between enrollment and 48 hours after drug administration will be tabulated.
Study Procedures	• **Retrospective analysis:** PDW data extracted and analyzed to determine incidence of respiratory depression, changes in slope at time of sugammadex introduction, and associations between reversal practices and time to discharge from the PACU. Propensity score for postoperative respiratory dysfunction created. • **Pathway creation and prospective pathway implementation:** Core group creates pathway guidelines and associated decision support. Build CDS pathway into EMR and collect data following go-live date. **CDS Pathway:** **Preoperative Phase**

		1) Physicians/CRNAs will receive an alert identifying the patient as high-risk for postoperative pulmonary complications and the reason for the designation. 2) The notification will remind the provider to pick up study sugammadex from the OR pharmacy. 3) The notification will display the patient specific lung protective ventilation (LPV) parameters.
		Intraoperative Phase
		1) There will be a notification reminding the provider to get the study sugammadex. 2) If the patient has mechanical ventilation and the parameters are outside the LPV guidelines (5-7cc/kg and at least 5 of PEEP) an alert will pop up with the LPV recommendations. 3) If non-depolarizing NMB was given and it has been more than 30 minutes since TOF was documented (and last documentation was <100% and no subsequent NMB was given), then a popup will recommend checking twitches (note we will have the twitch monitor automatically populate into CC). 4) Reverse with sugammadex.
Study Duration	The anticipated duration of subject participation in this study is 1 day (date of surgery).	

4.0 BACKGROUND AND RATIONALE

Postoperative respiratory dysfunction, as defined by requirements for supplemental oxygen, hypoxia, or (at its' most severe) reintubation is a known potential complication of general anesthesia[1,2]. Risk factors for this complication include airway surgery, multiple intubation attempts, and patient risk factors such as OSA or preexisting respiratory disease[3,4]. Previous work at our institution on nearly 23,000 patients in an ambulatory surgery center found that 28.7% of patients had at least one postoperative oxygen saturation less than 95%, and the hypoxia lasted for on average nearly 30 minutes; 1.5% of patients had at least one saturation less than 90%. While the etiology of this complication is multifactorial, one potential contributing factor is continued weakness due to residual neuromuscular blockade[5].

Neuromuscular blockade is used as part of general anesthesia in order to facilitate endotracheal intubation and help provide optimal surgical conditions[6]. While different classes of these drugs are used in clinical practices, data from our institution indicates that 55% of general anesthetics use rocuronium as a non-depolarizing neuromuscular blocking agent. In order to provide optimal surgical conditions for the duration of the surgery, but still allow for rapid emergence from anesthesia, it is common to use medications which pharmacologically "reverse" the neuromuscular blockade[7]. Traditionally, this was accomplished with neostigmine which serves to block cholinesterase and thereby increase the amount of acetylcholine available at the neuromuscular junction. More recently, sugammadex allows for the direct binding of rocuronium and a direct reversal of effect. This reversal is of faster onset and more effective than the use of neostigmine[8].



Preliminary data from our institution has shown that morbidly obese patients (which is highly correlated with obstructive sleep apnea) have a prolonged duration of desaturation and increased need for supplemental oxygen as compared to normal weighted controls. For example, the incidence of postoperative oxygen desaturation is 21% in those with a BMI between 18.5 and 25 but more than 40% in those with a BMI between 30 and 45. This results in an odd-ratio of 4.3 for patients with a BMI from 40 to 45 (see attached figure).

In order to facilitate the ability to perform this kind of data analysis, we have developed and maintain the Perioperative Data Warehouse (PDW), a custom-built data warehouse that facilitates the extraction of data from the Epic electronic medical record system (EMR)[9]. To date this infrastructure has been used in the publication of multiple studies in the peer reviewed literature[10-12], and we have been able to demonstrate that the automatic extraction of data from the EMR using this infrastructure is more accurate than manual chart review[12]. Querying of our data warehouse has demonstrated that 35.8% of patients who received intraoperative paralysis did not receive reversal of neuromuscular blockade; and, over the past year, of those who received reversal, 57.3% received sugammadex.

Our institution has not only built expertise in the extraction of data from the EMR, but also in the ability to implement effective real time perioperative clinical decision support (CDS). In one study, we have been able to integrate the reporting abilities of the PDW with the CDS capabilities of our EMR in order to provide perioperative reminders to provide adequate postoperative nausea and vomiting (PONV) prophylaxis to high risk patients. This intervention was successful at reducing the overall rate of PONV by 11% and the rate in high risk patients by 20%. Lastly, our department currently has several ERAS pathways that have been implemented. These include pathways for colorectal surgery, cystectomy and donor nephrectomy. In total approximately 300 patients have been involved in these pathways over the past year. We currently maintain automated dashboards that track the outcomes of patients in these pathways using our robust informatics infrastructure.

5.0 STUDY DRUG SUPPLY

Based on the retrospective phase of the study, on average 82% of patients received 200mg or less of sugammadex, 17% received between 200 and 500mg, and the remaining 1% received more than 500mg. The study drug supply will reflect these ratios; 80% of vials supplied will be 200mg, and the remainder will be 500mg vials.

6.0 STUDY DESIGN

In order to allow for a learning curve associated with the introduction of sugammadex we will not include any patients for one year after sugammadex introduction.

Creation and implementation of a pathway to prevent postoperative respiratory dysfunction:

In order to improve outcomes for high-risk patients who receive general anesthesia and paralysis we will design and implement a perioperative decision support system which will identify high-risk patients and provide best practice recommendations via electronic clinical decision support reminders. While the exact parameters of the pathway will be designed based upon feedback from a group of quality leaders in the department (see Study Procedures below), in general the pathway will function as follows.

Patients will be identified based upon the aforementioned selection criteria. Patients meeting one or more of the following:
Undergoing surgery at RRUMC OR, Santa Monica OR, obstructive or restrictive lung disease in EMR, obstructive sleep apnea, preoperative O2 saturation <95% (average/median of 12 hours before surgery), BMI>40, acute respiratory infection within 1 month prior to surgery, previous history of airway pathology; or two or more of the following: BMI>35, multiple intubation attempts, surgical duration >2 hours, upper abdominal surgery, intrathoracic surgery or airway/head and neck surgery, or most recent Hb (within 6 months) <10. Patients will be excluded if they are less than age 18, have co-existing renal disease with a GFR<30, neuromuscular disease, are pregnant or breastfeeding at the time of surgery, have an allergy to sugammadex or rocuronium, or patients who are expected to remain intubated after surgery or expected to leave the operating room with a tracheostomy in-situ.

When the anesthesiologist completes the preoperative evaluation for a patient who is flagged as having either respiratory disease or OSA and will receive general anesthesia, the anesthesiologist will receive a pop-up window reminding them of the best practice guidelines for pulmonary management in high-risk patients. As part of the study roll-out we will present these guidelines with our quality committee, but we anticipate that they will suggest 1) use of sugammadex to reverse neuromuscular blockade if rocuronium was used 2) use of objective train of four monitoring throughout the case and to confirm reversal 3) use of a tidal volume of 6-8 cc/kg 4) use of at least 5 cmH_2O of PEEP 5) positioning the head of the bed $>30^0$ after extubation.

7.0 SAMPLE SIZE

It is estimated that the respiratory depression pathway will recommend sugammadex for all patients in the medium or high-risk groups as well as some patients in the low risk group. The estimated anticipated sample size is 6,500 patients.

8.0 CLINICAL DECISION SUPPORT PATHWAY

The final clinical decision support pathway for clinician adherence involves preoperative and intraoperative phases. Clinicians will be trained prior to study go-live to ensure awareness and understanding of pathway procedures.

Preoperative Phase

1) Physicians/CRNAs will receive an alert identifying the patient as high-risk for postoperative pulmonary complications and the reason for the designation. 2) The notification will remind the provider to pick up study sugammadex from the OR pharmacy. 3) The notification will display the patient specific lung protective ventilation (LPV) parameters.
Intraoperative Phase
1) There will be a notification reminding the provider to get the study sugammadex. 2) If the patient has mechanical ventilation and the parameters are outside the LPV guidelines (5-7cc/kg and at least 5 of PEEP) an alert will pop up with the LPV recommendations. 3) If non-depolarizing NMB was given and it has been more than 30 minutes since TOF was documented (and last documentation was <100% and no subsequent NMB was given), then a popup will recommend checking twitches (note we will have the twitch monitor automatically populate into CC). 4) Reverse with Sugammadex.

9.0 STUDY HYPOTHESIS

1) Sugammadex is a direct reversal agent for rocuronium that has been shown to be superior to reversal with neostigmine. We hypothesize that the introduction of sugammadex into clinical practice at our institution results in a decrease in respiratory dysfunction in the PACU.
2) Creation and implementation of a pathway that applies best practices (including reversal with sugammadex) to patients who have obstructive sleep apnea (OSA), or preexisting respiratory disease will decrease the incidence of short-term respiratory complications

10.0 STUDY ENDPOINTS

Variables/Time Points of Interest

1) **PACU Discharge Time (primary endpoint):** The duration in minutes from patient arrival in PACU until the ready for discharge order is placed by the anesthesiologist. This captures the time until they are clinically ready for discharge and eliminates noise such as the availability of beds that might effect actual discharge time
2) **Incidence of oxygen saturation <90%:** A binary variable indicating if the patient had any oxygen saturations below 90% from arrival in PACU until being marked for discharge
3) **Incidence of oxygen saturation <95%:** A binary variable indicating if the patient had any oxygen saturations below 95% from arrival in PACU until being marked for discharge
4) **Duration of supplemental oxygen use in PACU:** The total time in minutes that a patient received supplemental oxygen from arrival in PACU until being marked for discharge
5) **Reintubation rate:** The incidence of patients who required reinsertion of an endotracheal tube after the patient was extubated in the OR. This includes patients who were reintubated in the PACU or subsequently after PACU discharge.
6) **Unplanned Upgrade of Care:** The incidence, defined as a binary variable, of patients who were transferred to an ICU after being admitted to a non-ICU setting.
7) **Obstructive Sleep Apnea (OSA):** The presence of obstructive sleep apnea based upon previous structured data in the electronic medical record (EMR) such as prescriptions for CPAP, medical history and the anesthesiologist's preoperative note.

11.0 STUDY POPULATION

UCLA RRUMC and UCLA Santa Monica patients aged 18 and older who had a general anesthetic with either rocuronium or vecuronium will be considered for inclusion in the study.

12.0 ELIGIBILITY CRITERIA

12.1 Inclusion Criteria

One or more of the following:

1	Undergoing surgery at RR OR, SM OR
2	Obstructive or restrictive lung disease in EMR
3	Obstructive sleep apnea
4	Preoperative O2 saturation <95% (average/median of 12 hours before surgery)
5	BMI > 40
6	Acute respiratory infection within 1 month prior to surgery
7	Previous history of airway pathology

Two or more of the following:

1	BMI>35
2	Multiple intubation attempts
3	Surgical duration >2 hours
4	Upper abdominal surgery, intrathoracic surgery, or airway/head&neck surgery
5	Most recent Hb (within 6 months only) <10

12.2 Exclusion Criteria

1	Pregnant or lactating (or gave birth within last year)
2	Age <18
3	Documentation of allergy or previous reaction to sugammadex
4	GFR <30
5	Neuromuscular disease (ICD codes)
6	Remain intubated/tach post-op

13.0 SUBJECT STATUS

Subjects will be classified as follows depending on their status:

- **Enrolled:** After meeting eligibility and being provided study drug from the OR pharmacy.
- **Withdrawn:** Meeting one of the conditions listed in the subject withdrawal section.
- **Subject completion:** Subjects will be considered to have completed this study upon successful confirmation of drug administration to the patient.

13.1 Subject Withdrawal

- Meeting any exclusion criteria that precludes subject's participation.
- In the Investigator's or IRB's opinion, a significant safety concern arises that requires subject discontinuation, or it is deemed that continued study participation is not in the subject's best interest.
- Study is terminated.

Investigators should follow withdrawn subjects with ongoing AEs until resolution according to standard of care.

13.2 Subject Discontinuation by Investigator

The Investigator, at their discretion, may discontinue a subject's enrollment into this study and/or withdrawal from the study. Should this occur, the reason for discontinuation will be documented onto the eCRF. All data collected prior to discontinuation may be used in the primary and secondary analysis.

14.0 SUBJECT RECRUITMENT

During the screening phase, patients aged 18 and older who will have a general anesthetic with either rocuronium or vecuronium and who are considered high risk for postoperative pulmonary complications will be flagged in CareConnect and enrolled in the study. Clinicians will receive an alert identifying the patient as a subject in the study and will remind the clinician to pick up the study drug sugammadex from the pharmacy.

15.0 HIPAA WAIVER OF AUTHORIZATION

Per the UCLA IRB, this study has received a HIPAA waiver of authorization for the entire study. PHI collected for the study from UC records will not be reused or disclosed, except in a de-identified format as indicated in the IRB.

16.0 INFORMED CONSENT PROCESS

This study has received a waiver of informed consent from the UCLA IRB, thus subject consent will not be required.

17.0 STUDY DATA COLLECTION

All aspects of the patient's management are at the discretion of the attending physician.

The following data will be collected and recorded in the eCRF:

Overall

- Admission ID
- Procedure name
- Primary CPT code
- Date of service
- UCLA location
- Case start time
- Case end time
- Procedure start time
- Procedure end time
- Emergency case status
- Case department name
- Obstructive respiratory lung disease
- OSA
- Preop SpO2
- BMI > 40
- Acute respiratory infection
- Airway pathology
- BMI > 35
- Multiple intubation attempts
- Surgery duration > 2 hrs
- Abdominal thoracic HN surgery
- Hgb less than 10 in 6 months
- Intraoperative sugammadex total?
- Sugammadex administered time
- Flag pushed in from PDW
- BPA fired in Epic
- Received rocuronium intraop
- Received study drug
- Enrolled patient
- PACU signout time
- Duration O2 saturation less than 90%
- Duration O2 saturation less than 95%
- Pathway compliance
- Postop reintubation
- Unplanned upgrade of care
- EARS study drug
- Inpatient death
- Bradycardia
- Anaphylaxis
- Reintubation

Baseline data

- Age

- Weight
- BMI
- ASA Physical Status Score
- Number of STOP Bang Criteria
- Existence of OSA on Problem List
- Previous Charting for OSA
- Previous Prescription for CPAP/BiPAP
- Lung Disease in problem list
- Abnormal PFT results
- Previous coding of lung disease
- Surgical procedure
- Oxygen saturation in preoperative area
- Preoperative Hemoglobin

Intraoperative Data

- Surgical duration
- Median PEEP
- Median TV
- Median FiO2
- Maximum PEEP
- Maximum TV
- Maximum FiO2
- Minimum PEEP
- Minimum TV
- Minimum FiO2
- Time and dosage of administration of rocuronium
- Time, dosage and name of reversal agent
- All documented assessments of muscle strength (i.e. TOF ratio)
- Anesthesia Provider
- Time since most recent dosage of neuromuscular blocking agent
- Most recent train-of-four ratio prior to reversal.

PACU Data

- Time until ready to discharge
- Duration of supplemental oxygen therapy
- Minimum oxygen saturation
- Duration of oxygen saturation <95
- Duration of oxygen saturation <90
- Adverse events and protocol deviations, if applicable

18.0 SAFETY AND ADVERSE EVENTS

18.1 Definitions

The definitions for adverse event, serious adverse event, and unanticipated adverse effect are provided below.

18.2 Adverse Event (AE)

Adverse event shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

18.3 Serious Adverse Event (SAE)

Serious adverse event shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered “serious”.

18.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction or “SUSAR” shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator’s brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

18.5 Sugammadex Common Adverse Reactions

Sugammadex is an FDA-approved drug. The Merck prescribing information for Bridion (sugammadex) includes vomiting, pain, nausea, hypotension, and headache as the most common adverse reactions reported. In a small number of patients, the following known outcomes have occurred: anaphylaxis and marked bradycardia.

The list of SAEs and SUSARs for study reporting includes:

- Unplanned upgrade of care
- Unexpected transition in patient status
- Reintubation
- Bradycardia
- Anaphylaxis
- Death

19.0 RECORDING OF ADVERSE EVENTS

- All Adverse Events occurring within 48 hours of drug administration, regardless of seriousness, severity or relationship to the study drug, must be recorded in the eCRF and will include a detailed event description, date of onset, date investigator first aware, whether the event is serious, investigator's assessment of severity, relationship to study drug, action taken with respect to the study drug, corrective treatment/therapy given, additional assessments performed, outcome, and date of resolution/stabilization of the event.
- Any pre-existing medical condition that is present at the time of screening will not be reported as an AE, unless the condition worsens during the course of participation. The occurrence of diagnostic or elective surgical procedures for a pre-existing condition will not be recorded as an AE, unless the condition becomes more severe or results in an AE.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms.
- The investigator should take appropriate measures to follow all AEs until resolution or until progression has been stabilized, or until study exit, to ensure the safety of the subjects. If the AE continues beyond the period of subject enrollment in the study and/or the date the subject withdraws from the study, clinical investigators should follow the subjects according to standard of care.
- All SAEs will be followed until the Investigator deems the event to be chronic or the adherence to be stable or until the subject exits the study. Other supporting documentation of the event may be requested by the Sponsor and should be provided as soon as possible.
- All subject deaths, regardless of relationship to the study drug, should be reported.
- Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented based on the system organ class and preferred term.

20.0 Guidelines for Reporting AE

20.1 Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction Reporting to Sponsor

Principal Investigator shall forward to Merck's Global Pharmacovigilance ("Merck GPV") group, any SAE or SUSAR, including, but not limited to, all initial and follow-up information involving any Study subject in the Study. Notification shall be in the form of a completed CIOMS I/MedWatch (or other mutually agreed upon format) **within two (2) business days of but not longer than three (3) calendar days of receipt of the information**. This information shall be transmitted to Merck GPV using the contact information provided below or such other modified contact information as provided by Merck in writing. All information shall be transmitted in the English language and contain the reporter's name and the Study subject identifier code. SUSAR information will be reported unblinded if the Study Drug has been blinded in the Study. Randomization codes for all other SAEs will be provided to Merck GPV at end of Study if the Study Drug has been blinded in the Study.

All reports of Study Drug exposure during pregnancy or lactation, whether associated with an AE or not, must be reported to Merck GPV in accordance with the timelines and contact information for an SAE. Principal Investigator shall follow pregnancies to term to obtain the outcome of the pregnancy. The outcome of the pregnancy shall be forwarded to Merck GPV.

Institution and Principal Investigator shall fully comply with all of their respective reporting obligations to the applicable regulatory authorities with respect to any AE, SAE or SUSAR that arises from the Study.

SAE reports and any other relevant safety information are to be forwarded to Merck GPV facsimile number: 215-661-6229.

20.2 POST-APPROVAL (PA) REPORTING TO THE IRB

The PI must report to the IRB adverse events that meet all three of the following criteria

- Unexpected;
- Related or possibly related to research participation; and
- Places participants or others at greater risks of harm than was previously known or recognized (not described in or of greater severity or frequency than described in the IRB-approved protocol and/or consent form)

In reviewing (internal or external) adverse events, the IRB ***may request additional follow-up information***. These can include autopsy results or terminal medical reports for an unexpected study-related death.

For all adverse events (internal or external) that meet the above criteria, the IRB ***may require additional action*** in response to the event in order to ensure that the research continues to meet the criteria for approval under 45 CFR 46.111 and/or 21 CFR 56.111. This may include:

- revision of the consent form to include risk(s) identified as a result of this event
- re-consent of enrolled participants continuing study treatment
- notification to previously enrolled participants and/or participants in long-term follow-up
- protocol changes to address and minimize newly identified risk(s)
- suspension of enrollment or all study procedures
- termination of the research

Those AEs that the IRB agrees meet the above criteria will receive the determination of *Unanticipated Problems involving risks to subjects or others* under 45 CFR 46.108(a)(4)(i), 21 CFR 56.108(b)(1), 21 CFR 312.53(c)(1)(vii) and/or 21 CFR 312.66.

- The IRB will report that determination to the appropriate federal department(s) and UCLA institutional officials as required.

Initial and follow-up reports of AEs that meet the reporting criteria should be submitted to provide the IRB with complete information on the adverse event. Adverse event findings associated with the study drug will be followed until the event resolves or stabilizes at a level acceptable to the Principal Investigator.

20.3 DEADLINES FOR SUBMISSION TO THE IRB

- **Within 3 business days of learning of the event:** *Internal or External Adverse events meeting the above criteria resulting in **death, suspension, suspension** or **termination of the research***
- **Within 10 business days of learning of the event:** All other *reportable adverse events meeting the above criteria*

- No PAR submission (maintain in study files):
  - Internal or external adverse events that ***do not meet*** the above criteria
  - External AEs where the investigator ***does not yet know*** whether or not the event placed the participants or others at increased risk
  - Follow-up reports of external AEs that do not provide information on increased severity of the event since the initial report to the IRB
- No PAR submission (summarize at continuing review):
  - Deaths that are related and expected

All Adverse Events must be reported to the Sponsor and IRB in accordance with the following timeline:

Type of Reportable Event	Reporting Schedule to Sponsor	Reporting Schedule to IRB
AE		Follow local IRB reporting requirements as discussed in section 20.3
SAE	Within 2 calendar days or 3 days total after the Investigator is first aware.	SAE / Patient death shall be reported in accordance with local requirements.
SUSAR	Within 2 calendar days or 3 days total after the Investigator is first aware.	SAE / Patient death shall be reported in accordance with local requirements.

The study Sponsor will report safety events to the FDA as required per 21 CFR 812. Sponsor reporting requirements are as follows:

- The PI is responsible for classification of adverse events, reviewing investigators' assessment of adverse events, and reporting to IRBs and regulatory agencies, and to Data Safety Monitoring Committee. If results of the

evaluation of an unanticipated adverse effect were determined to be an unreasonable risk, the PI shall notify the IRB, and participating investigators within 10 working days after the Sponsor first receives notice of the unanticipated adverse effect. The IRB is responsible for informing regulatory agencies if an AE meets the criteria listed in 20.2 and it receives the determination of Unanticipated Problems involving risks to subjects or others.

22.0 PROTOCOL DEVIATIONS ("PD")

All efforts should be made to avoid any protocol deviation. Any deviation from the requirements outlined in this protocol will be considered a protocol deviation. A protocol deviation that may affect the scientific soundness of the protocol or the rights, safety, or welfare of the patients should be reported to the IRB and applicable regulatory authorities. Other deviations are those that occur in direct association with a specific study patient. These include, but are not limited to, deviations from inclusion/exclusion criteria, protocol-specified procedures and assessments, and study drug handling and usage. All protocol deviations and their reasons will be reported to the study sponsor, documented in the eCRF and protocol deviation log.

23.0 GUIDELINES FOR REPORTING PDS TO THE IRB

Investigators are required to keep a log of all deviations/Incidents.

Only the subset of those deviations that the PI determined have affected the rights and/or welfare of participants or others must be submitted to the IRB for review. However, the entire log may be reviewed by OHRPP Quality Improvement Unit (QIU) and the log should be submitted at continuing review for those studies that are subject to continuing review.

The following information/assessments should be recorded in the Investigator's deviation/incident log:

- Date of event
- Subject ID
- Date the investigator was made aware of the event
- A description of the event
- Is this an initial event or a follow-up/update on a previous event?
- Does the deviation meet the threshold for reporting to the IRB?
- Who (which member of the study team) made the assessment of whether or not the deviation met the threshold for IRB reporting via PAR?
- Date the assessment made (of whether it met the threshold for IRB reporting via PAR)
- Date of submission to the IRB (if applicable)
- PAR# (if applicable)

A subset of deviations/incidents must be submitted via PAR application for timely review:

Deviations/incidents for which the answer to any of the following questions is "yes" should be submitted to the IRB for review via PAR application:

1) Did the deviation/incident cause the participant or someone else to be at risk of potential harm?
2) Was the participant or someone else actually harmed by the deviation/incident?
3) Does the deviation/incident negatively affect the rights of participants or others?
4) Does an individual deviation not meet the above criteria, but there are 4 or more of the same type of minor deviation in a study and those deviations, taken as a group, suggest a pattern of non-compliance on the part of the study team or ancillary staff?
5) Does an individual deviation not meet the above criteria, but there are 4 or more of the same type of minor deviation in a study and those deviations, taken as a group, suggest a pattern of non-compliance on the part of the study team or ancillary staff?

Root cause Analyses

For all PAR applications describing deviations that meet the criteria for reporting (either single occurrence or aggregate) the investigator should conduct a quality improvement review that includes a root cause analysis. This is necessary to determine if there are underlying systems problems that led to this deviation.

Corrective Action Preventive Action (CAPA) plan

Once a root cause has been identified, a CAPA plan must be developed by the investigator and included in materials submitted to the IRB. The CAPA should address two areas:

1) How will the deviation be resolved for the participant(s) who has already experienced the event? (does the participant require additional monitoring, should the participant be informed, does the participant need to be approached for re-consent or be asked to provide HIPAA authorization, etc.)
2) How will research procedures be modified to prevent similar deviations in the future? (does the study need an eligibility checklist, should the order process with pharmacy for study drug be updated, do study team members with greater clinical experience need to administer instruments, etc…)

For deviations related to HIPAA authorizations or breach of confidentiality for UCLA Health- related research records, study team will consult with UCLA Health Office of Compliance Services to develop the CAPA plan. The CAPA developed with UCLA Health Office of Compliance Services must be provided to the IRB for a final determination

24.0 WITHDRAWAL OF IRB/EC APPROVAL

An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible.

25.0 POWER ANALYSIS AND SAMPLE SIZE DETERMINATION

25.1 Retrospective analysis

In order to assess the change in time to readiness for PACU discharge and postoperative respiratory dysfunction (duration of oxygen saturation below 90%) after the introduction of sugammadex we will construct two models. First, we will utilize propensity score matching (PSM)[14] to adequately risk balance the patients pre/post sugammadex introduction (variables mentioned in section 2.4). We will use the nearest-neighbor PSM approach and start with a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score (as described by Austin[15]). We will assess balance of the covariates pre/post intervention by computing

standardized mean differences (SMD) for each variable and will use the rule of thumb "SMD less than 0.1"[16] to indicate adequate balance. Finally, we will also construct a table of patient characteristics pre/post matching to see how well the algorithm balanced the patients. If individual covariates are not adequately balanced with the default propensity score matching algorithm, we will try different matching parameters until adequate balance is achieved (e.g. change the caliper size for what we consider a match and/or run a more advanced propensity score model including interaction or squared terms.

After adequate balance is observed, we will compare our outcomes of interest between pre/post periods using a linear (or log-linear) model for time to readiness and logistic regression for our binary outcome (postoperative respiratory dysfunction) using the propensity matched dataset. An interrupted time-series (also known as segmented regression) analysis as described by Wagner[17] will be conducted for each outcome to estimate the pre-intervention time trend, immediate impact of intervention (change-point), as well as reliably estimating the slope change after the intervention. All estimates of interest from these models will be summarized with p-values and 95% confidence intervals.

Statistical analyses will be performed using R V3.5.1 (Vienna, AU) using the "*Match*" package for propensity score matching and p-values <0.025 (for our two primary outcomes) will be considered statistically significant utilizing the Bonferroni adjustment (0.05/2).

25.2 Prospective analysis

The prospective analysis will largely follow a similar framework however we will focus on the primary and secondary outcomes as described above and will use a one year period prior to implementation as our baseline.

26.0 ESTIMATED SAMPLE SIZE

Sugammadex was introduced into clinical practice at UCLA in May of 2016, thus we have well more than one year of data prior to and after sugammadex introduction. As a result, the power analysis and sample size discussion is roughly the same for the retrospective and prospective portions of this study.

Over the previous one year period, approximately 13,000 patients received general anesthesia with the use of either rocuronium or vecuronium. Given that our surgical volumes are stable we would expect the sample size for the prospective portion of our study to be roughly the same. The table below contains the risk stratification for this group.

To determine the study power, we analyzed the incidence of the primary and secondary outcomes for our historical population. Because there is no current pathway, we are unable to explicitly model the power for performance of identified best practices however the power for the primary outcome as well as secondary outcomes were calculated.

In order to determine our power for the study variables patients were separated into low, medium, and high-risk groups. Low risk patients were those who had no prior documentation of OSA or respiratory disease prior to surgery. Medium risk patients were those with either OSA or respiratory disease and high risk patients were those with both diseases. It is important to note that this classification is significantly simplified as compared to the analysis that will be performed for either the retrospective or prospective studies as it fails to account for key factors such as severity of illness. Nonetheless we believe that these simplifications have the effect of underestimating the potential power and thus the below serves as a conservative estimate.

Table 1. Number of patients in low, medium, and high risk groups from 12/2017- 11/2018	
Risk Class	**Number of Patients**
Low – No disease	9730
Medium – OSA or Respiratory Disease	2952
High – OSA and Respiratory Disease	445
Total	**13,127**

Note: The risk classifications above are simplified versions of the true risk classifications to be used in the actual study

At this point, we estimate that the pathway will recommend sugammadex for all patients in the medium or high-risk groups as well as some patients in the low risk group (i.e. those patients requiring deep neuromuscular blockade to facilitate surgical conditions such as robotic procedures, free flap cases and others). Given the large number of patients, Merck would supply one vial of study drug for each patient. Thus the total amount of study drug would be no more than 6,500 patients for the one year intervention time.

Given 1 year of data, we observed an overall average PACU discharge time of 152.54 minutes (SD=623.86). With one year of post-data, we are adequately powered (90%) to pick up a reduction in PACU discharge time as small as 27.04 (two-sample t-test, alpha=0.025). Since the current difference in PACU discharge time between low and high risk groups is 67.52 (subtracting 216.62-149.10, see table), we feel the 27.04 minimally detectable difference gives us a great chance of detecting a meaningful difference.

Given 1 year of data (pre-period), we observed the rate of patients with any time SpO2<90% was 4.6% (574/12,467). With one year of post-data, we are adequately powered (90%) to pick up a reduction in this rate if it decreases to around 3.7% in the post (chi-square test, alpha=0.025). Since the current difference in patients with any time with SpO2<90% between low and high risk patients is 5.2% (subtracting 9.2%-4.0%), we feel the minimally detectable difference of 3.7% (4.6%-3.8%) is feasible.

Table 2.

	suppl O2, mean (SD)	**PACU disch. Time, mean (SD)**	**Reintubation, freq (%)**	**Unplanned upgrade, freq (%)**	**SpO2<90%, freq (%)**	**SpO2<95%, freq (%)**
OVERALL(n=13,277)	**74.81 (241.82)**	**152.54 (623.86)**	**89 (0.7%)**	**138 (1.0%)**	**574 (4.6%)**	**6510 (52.3%)**
low (n=9,841)	**74.48 (280.55)**	**149.10 (599.78)**	**63 (0.6%)**	**111 (1.1%)**	**372 (4.0%)**	**4603 (50.0%)**
medium(n=2,997)	**74.98 (95.67)**	**154.43 (536.58)**	**23 (0.8%)**	**22 (0.7%)**	**164 (5.8%)**	**1658 (58.8%)**
high (n=439)	**79.54 (88.44)**	**216.62 (1321.46)**	**3 (0.7%)**	**5 (1.1%)**	**38 (9.2%)**	**249 (60.9%)**
Smallest detectable difference (90% power)	**9.61**	**24.84**	**0.4%**	**0.4%**	**3.8%**	**50.3%**

27.0 EARLY STOPPING RULES

Upon review of occurrence of unanticipated adverse drug effects and/or other harmful events as a direct result of the clinical study procedures, the principal investigators, sponsor, and DSMB may decide to:

1. Terminate the study to safeguard subject safety.
2. Stop the recruitment
3. Continue with the recruitment

28.0 RISK/BENEFIT ASSESSMENT

28.1 Risks

Sugammadex is an FDA approved drug. Adherence to the CDS pathway and administration of sugammadex will be at the discretion of the clinician. Thus, study risks are very limited.

28.2 Benefits

All participants in the study may benefit from additional assessments (e.g., additional bloodwork) obtained as part of study procedures.

29.0 STUDY MANAGEMENT

29.1 Selection and Training of Clinical Investigators

The sponsor will keep on file a list of names of all investigators involved in the study. The study will not use, in any capacity, the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this clinical study.

Sponsor personnel or designee will provide all clinical investigators with training on use of the study drug prior to their participation in the clinical study.

The study staff involved will undergo site initiation and training, which will include:

- Study protocol
- Consenting procedures and Human Subjects Protection
- Directions for use
- Investigator responsibilities, including reporting requirements
- Monitoring and auditing
- eCRF completion guidelines
- EDC system

- Electronic recordkeeping
- Study drug accountability procedures
- Protection of subject confidentiality

New members of the clinical site team may be added from time to time at new or existing sites. New personnel should only start their assignment after receiving adequate training in the clinical investigation requirements and this training shall be documented. The names, initials, signatures, functions, and designated authorizations of new site personnel shall be documented.

29.2 Data Management

29.2.1 Electronic Data Capture (EDC)

All data is extracted from the Perioperative Data Warehouse (PDW), a custom built warehouse that extracts data from the EPIC EHR's Clarity Database. After the extraction the data is cleaned and organized in a way that mirrors clinical concepts and facilitates reporting. For each element in the study, an algorithm is built that extracts the necessary raw clinical data and determines the element of interest. A table of these elements is then stored in the PDW and delivered to the study team on a regular basis.

29.2.2 Data Cleaning

Data from the EHR is cleaned at three levels. First, in extracting the data from the EHR multiple tables are combined and concepts are joined to deal with both missing and duplicate data. Second, upon extraction from the EHR standardized keys are used to unify commonly used values such as lab results, medications, etc. Lastly, each of the final elements used in the study are created from multiple raw data points in order to deal with missing and erroneous data. In particular, decisions are made for sensitivity vs precision in order to ensure optimal data capture

The database will be subject to inspection for omitted data, gross data inconsistencies, and deviations. Any deficiencies or deviations will be reviewed, and any necessary action determined (e.g., data query, communication with the study center).

Intermittent data review will be performed, and any discovered errors will be reported to the study site using the electronic query process (as necessary). The study site will be expected to review and complete the query. The data cleaning cycle will be repeated until all data are considered clean.

29.3 Data Back-up, Confidentiality and Security

All data are stored and maintained on servers operated by the UCLA Health Office of Health Informatics and Analytics (OHIA). These servers are maintained behind the UCLA Health firewall and only accessible via a Citrix environment secured by two factor authentication. Whenever possible data for the study are extracted in a fully deidentified manner and only delivered to the study team via secure methods. All data extracts are logged and audits are periodically performed to ensure compliance.

29.4 Data Safety Monitoring Plan

29.4.1 Protection of Subject Privacy

During the study, all data will be collected only in already existing databases. For analysis and reporting purposes, data will only be extracted in the aggregate or in a de-identified dataset.

29.4.2 Database Protection

The database containing patient data will be housed on an OHIA maintained server and secured with password and two-factor authentication. Retrieval of data for analysis will be performed by informatics personnel not on the study team.

29.4.2 Confidentiality During Adverse Event Reporting

AE reports and annual summaries will not include subject- or group-identifiable material. Each report will only include the identification code.

29.4.3 Data Quality and Management

Data for the study will be obtained by automated extraction from the Perioperative Data Warehouse (PDW), the Department of Anesthesiology's Reporting database. Phenotypes for patient risk factors, compliance with best practice pathways and postoperative outcomes will be created using standardized procedures that have been previously reported in the literature. In order to ensure accuracy a subset of cases will be randomly selected for manual review to ensure data accuracy.

The research pharmacy will maintain records of which patients were administered study drug (a criteria for patient inclusion) and these data will be delivered to the study team as an Excel file. These data will be uploaded into the PDW for cross-referencing with the EHR.

29.4.4 Subject Accrual and Compliance

Reports of patients who meet the clinical inclusion criteria and who did and did not receive study drug will be reviewed weekly for the first 2 months of the study and then monthly thereafter to ensure adequate patient recruitment.

29.5 Quality Assurance and Auditing

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. The sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve subject confidentiality.

The study site is subject to audit by study sponsor personnel or designee for protocol adherence, accuracy of eCRFs and compliance with applicable regulations. The sponsor will communicate to the sites any patterns of non-compliance. The sponsor will work with the sites to determine any necessary corrective action, as applicable. The study protocol, data-recording procedures, data handling and study reports are subject to an independent clinical Quality Assurance audit by sponsor, its designee, or health authorities.

30.0 INVESTIGATOR RESPONSIBILITIES

30.1 General Responsibilities

- Each investigator is responsible for i) ensuring that an investigation is conducted per the signed investigator statement (Investigator Agreement/Commitment), the study protocol, and applicable regulations, ii) protecting the rights, safety, and welfare of study subjects under the investigator's care and iii) controlling drugs under investigation.
- The investigator shall assure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports.
- Each investigator (or designee) is responsible for all applicable IRB requirements under 21 CFR Part 56 and ISO14155.
- Each investigator is responsible for disclosure of financial obligations/conflict of interest to the sponsor in accordance with provisions of 21 CFR Part 54.
- The study will be conducted under 21 CFR 11, 50, 54, 56, 812 and ISO14155. Investigators will be trained on their responsibilities.
- To ensure proper execution of the study protocol, each investigator will identify study coordinators for this study. Working with and under the oversight of the principal investigator, the study coordinators ensures that all study requirements are fulfilled.
- Each investigator will allow monitoring and auditing of their clinical investigation procedure(s) by the sponsor or designee.

30.2 Good Clinical Practice

ICH E6 Good Clinical Practice guidance is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

It specifies general requirements intended to:

- Protect the rights, safety and well-being of human subjects,
- Ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,
- Assist Sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of drugs.

The Principal Investigator of the clinical investigation shall:

- Obtain and maintain IRB/EC approval of the study.
- Ensure only appropriately trained personnel will be involved in clinical investigation.
- Maintain study records mentioned in the protocol.

- Maintain logs for study team delegation, site visit/monitoring, equipment disposition, study team training, subject recruitment and enrollment.
- Evaluate all adverse events and determining whether the study is safe to continue.
- Allow the Sponsor to conduct periodic monitoring of study activities to ensure GCP compliance.

The Sponsor shall ensure existence and record of all necessary compliance documents, and will conduct monitoring visits to ensure appropriate conduct of the study.

30.3 Provisions to Protect the Privacy Interests of Subjects

Per FDA guidance, a waiver of informed consent may be used for clinical research involving minimal risk. This study has received a waiver of informed consent for the entire study through an approved UCLA IRB application.

Prior to the start of data collection or subject enrollment, the Investigator must provide documentation of IRB approval of the study protocol.

All subjects will be monitored closely throughout the study. The following measures will be taken to ensure the privacy of subjects:

- Subject data will be fully de-identified via an honest broker. Only the honest broker will have access to identifiable patient data for the study.
- Access to the documents and data will only be made to the Investigators and study staff in the study.
- The confidentiality of these documents will be protected to the extent provided by the law.

30.4 Maintenance and Retention of Study Records

The PI is required to maintain adequate and accurate study records in accordance with Sponsor requirements.

The PI shall have the following record keeping and reporting obligations:

preparation and maintenance of written records in accordance with laws, regulations and good clinical practice;

a Study manuscript, which would be appropriate for submission to a peer reviewed journal, provided to Merck within one-year from the final subject being examined or receiving an intervention for the purposes of final collection of data of the Study regardless of the Study results;

preparation and submission of periodic progress reports every three (3) months via the Merck grant management web site or, if the Parties can agree to an alternative format, such format as the Parties have otherwise mutually agreed upon in writing (failure to provide progress reports may result in immediate termination of this Agreement); and

A final study report summarizing the Study results and conclusions reached by Institution within a reasonable time after completion of the Study but in no event longer than six (6) months after completion of the Study. The final study report shall be made of descriptive data, tables, and data listings, and contain all relevant adverse experiences as a line listing or

table. Any Study subject level data submitted to Merck will only be coded with a number and no other personal identifiers such as birth date or Study subject initials

30.5 Institutional Review Board Approval

Institutional Review Board ("IRB") approval of study protocol and ICF is required prior to study commencement under 21 CFR Part 56. The sponsor's justification of the non-significant risk determination of the study and any supporting information, as necessary, will be provided to the IRB under 21 CFR 812.2(b). Clinical investigators must also obtain renewal of IRB approval throughout the duration of the study. Clinical investigators are responsible for fulfilling any conditions of approval imposed by the reviewing IRB, such as regular reporting, study timing, etc. Clinical investigators will provide the study sponsor with copies of such approvals and reports.

30.6 Required Documentation from Sites

At a minimum, the following documents will be stored by the study site:

- IRB study approval letter
- Fully executed clinical trial agreement (CTA)
- Investigator agreement/commitment for the participating investigator(s)
- Financial disclosure form for the participating investigator(s)
- Curriculum vitae (CV) for the participating investigator(s)
- Current medical license for the participating investigator(s)
- Principal investigator protocol acknowledgement form

31.0 PROTOCOL AMENDMENTS

Any changes made to the clinical investigational plan/study protocol will be documented by way of an amendment. The Investigator shall not make any changes to the protocol without Sponsor approval and documented approval from the IRB. The PI will retain the IRB approval letter and approved protocol as confirmation that the protocol amendment was approved.

32.0 SUSPENSION OR TERMINATION OF STUDY SITE

The Sponsor can suspend or pre-maturely terminate the PI's and study site's participation in the study, particularly if the Sponsor finds serious non-compliance by the PI or site, and if such non-compliance was not resolved in a timely and appropriate manner. The Sponsor will document the decision to suspend or terminate the investigation in writing. A suspended study site cannot enroll new subjects.

If the Sponsor determines that the study site's compliance to GCP and federal regulations to be inadequate at any point during the study, and the Sponsor moves to suspend or terminate the study site, the Sponsor will provide notification in writing to the principal investigator and IRB as necessary. The study site is eligible for re-instatement upon correction of

any findings and any open action items prior to the suspension, and provides a written guarantee that the same non-compliance will not re-occur in the future. Site can only resume patient enrollment upon patient enrollment upon receiving written notification of re-instatement from the Sponsor and/or the IRB.

33.0 TERMINATION OF CLINICAL INVESTIGATION/STUDY

The clinical investigation may be terminated if Sponsor determines that an unanticipated adverse drug effect presents an unreasonable risk to the subjects, obtaining new scientific knowledge that shows the study is no longer valid, insufficient recruitment of subjects, or at the discretion of the study Sponsor, IRB, or other regulatory body. In the event Merck or Institution believes that immediate termination is necessary due to its evaluation of risks to enrolled subjects, Merck or Institution may terminate the study immediately.

34.0 PUBLICATION AND DATA SHARING POLICY

All Study data and results will be owned by Institution. Institution agrees that all reports and compilations of data required to be delivered to Merck under the Protocol or this Agreement, and all Study data and results (excluding protected health information, patient medical records and all original source documents) as contained therein generated in the course of the Study ("Study Reports") may be used fully by Merck for any legitimate business purpose without any additional payments being made to Institution, subject to applicable regulations and laws. Institution does not promise any particular results from the Study and makes no representation or warranty of any kind, expressed or implied, with respect to the Study results. Merck agrees not to publish or otherwise disclose the Study Reports and any portion of the research data and results contained therein generated during the course of the Study until Institution's publication or presentation of the Study results in accordance with this Article 9, or eighteen (18) months following completion of the Study or termination of this Agreement, whichever occurs first. Notwithstanding anything to the contrary, Merck may disclose the research data and results to applicable federal, state or local health authorities provided if such disclosure is prior to Institution's publication Merck shall use reasonable efforts to disclose such research data and results contained therein confidentially and shall give Institution reasonable advance written notice of the required disclosure. Institution agrees not to provide any competing commercial third party with access to or with the right to use the data or results for any purpose until publication as set forth herein without the written permission of Merck, which shall not be unreasonably withheld.

35.0 REFERENCES

1. International Surgical Outcomes Study group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. British Journal of Anaesthesia 2016;117:601–9.
2. Hafeez KR, Tuteja A, Singh M, Wong DT, Nagappa M, Chung F, Wong J. Postoperative complications with neuromuscular blocking drugs and/or reversal agents in obstructive sleep apnea patients: a systematic review. 2018:1–11.
3. Nagappa M, Subramani Y, Chung F. Best perioperative practice in management of ambulatory patients with obstructive sleep apnea. Current Opinion in Anaesthesiology 2018:1–7.
4. Gali B, Whalen FX, Schroeder DR, Gay PC, Plevak DJ. Identification of patients at risk for postoperative respiratory complications using a preoperative obstructive sleep apnea screening tool and postanesthesia care assessment. Anesthesiology 2009;110:869–77.

5. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual Neuromuscular Blockade and Critical Respiratory Events in the Postanesthesia Care Unit. Anesthesia & Analgesia 2008;107:130–7.
6. Pühringer FK, Khuenl-Brady KS, Koller J, Mitterschiffthaler G. Evaluation of the endotracheal intubating conditions of rocuronium (ORG 9426) and succinylcholine in outpatient surgery. Anesthesia & Analgesia 1992;75:37–40.
7. Brull SJ, Murphy GS. Residual Neuromuscular Block. Anesthesia & Analgesia 2010;111:129–40.
8. Sparr HJ, Vermeyen KM, Beaufort AM, Rietbergen H, Proost JH, Saldien V, Velik-Salchner C, Wierda JMKH. Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomized multicenter study: efficacy, safety, and pharmacokinetics. Anesthes 2007;106:935–43.
9. Hofer IS MD, Gabel E, Pfeffer M MD, Mahbouba M MD MS, Mahajan A MD PhD. A Systematic Approach to Creation of a Perioperative Data Warehouse. Anesthesia & Analgesia.
10. Hofer IS MD, Cheng D, Grogan T, Fujimoto Y, Yamada T, Beck L, Cannesson M, Mahajan A MD PhD. Automated Assessment of Existing Patient's Revised Cardiac Risk Index Using Algorithmic Software. Anesthesia & Analgesia 2018.
11. Lee CK, Hofer I, Gabel E, Baldi P, Cannesson M. Development and Validation of a Deep Neural Network Model for Prediction of Postoperative In-hospital Mortality. Anesthesiology 2018;129:649–62.
12. Gabel E, Hofer IS MD, Satou N, Grogan T, Shemin R, Mahajan A MD PhD, Cannesson M. Creation and Validation of an Automated Algorithm to Determine Postoperative Ventilator Requirements After Cardiac Surgery. Anesthesia & Analgesia 2017;124:1423–30.
13. Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. British Journal of Anaesthesia 2012;108:768–75. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3325050&tool=pmcentrez&rendertype=abstract.
14. ROSENBAUM PR, RUBIN DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
15. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharmaceut Statist 2011;10:150–61.
16. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Statist Med 2007;26:734–53.
17. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27:299–309.

36.0 APPENDIX A - LIST OF STUDY INVESTIGATORS

Sites and investigators subject to IRB approval and subject to change without requiring protocol amendment.

Principal Investigator	Eilon Gabel, MD Dept. of Anesthesiology and Perioperative Medicine Ronald Reagan Hospital, University of California Los Angeles Email: egabel@mednet.ucla.edu
Other Site Investigators	John Shin, MD
	Theodora Wingert, MD
	Emily Methangkool, MD PhD
	Carol Lee
Study Coordinators	Stephanie-Dee Sarovich
	Olivia Vallejo

Statistical Analysis Plan

Variables/Time Points of Interest

Overall a variety of variables may be used for patient risk stratification, or creation of the propensity score. The majority of these have standard definitions and are listed above. The list below includes key variables used as inclusion criteria and or outcomes.

•PACU Discharge Time (primary endpoint): The duration in minutes from patient arrival in PACU until the ready for discharge order is placed by the anesthesiologist. This captures the time until they are clinically ready for discharge and eliminates noise such as the availability of beds that might effect actual discharge time

•Incidence of oxygen saturation <90%: A binary variable indicating if the patient had any oxygen saturations below 90% from arrival in PACU until being marked for discharge

•Incidence of oxygen saturation <95%: A binary variable indicating if the patient had any oxygen saturations below 95% from arrival in PACU until being marked for discharge

•Duration of supplemental oxygen use in PACU: The total time in minutes that a patient received supplemental oxygen from arrival in PACU until being marked for discharge

•Reintubation rate: The incidence of patients who required reinsertion of an endotracheal tube after the patient was extubated in the OR. This includes patients who were reintubated in the PACU or subsequently after PACU discharge

•Unplanned Upgrade of Care: The incidence, defined as a binary variable, of patients who were transferred to an ICU after being admitted to a non-ICU setting.

•Obstructive Sleep Apnea (OSA): The presence of obstructive sleep apnea based upon previous structured data in the electronic medical record (EMR) such as prescriptions for CPAP, medical history and the anesthesiologist's preoperative note.

•Preexisting respiratory disease: The presence of obstructive or restrictive lung disease as defined based on the structured data in the EMR such as previous PFT results, previous medication and previous diagnoses. For analysis purposes patients will be divided into low, medium and high risk groups based on the extent of their disease.

Statistical Methods:

All analysis will be performed by the study team at UCLA.

Retrospective analysis: In order to assess the change in time to readiness for PACU discharge and postoperative respiratory dysfunction (duration of oxygen saturation below 90%) after the introduction of sugammadex we will construct two models. First, we will utilize propensity score matching (PSM) to adequately risk balance the patients pre/post sugammadex introduction. We will use the nearest-neighbor PSM approach and start with a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score. We will assess balance of the covariates pre/post intervention by computing standardized mean differences (SMD) for each variable and will use the rule of thumb "SMD less than 0.1" to indicate adequate balance. Finally, we will also construct a table of patient characteristics pre/post matching to see how well the algorithm balanced the patients. After adequate balance is observed, we will compare our outcomes of interest between pre/post periods using a linear (or log-linear) model for time to readiness and logistic regression for our binary outcome (postoperative respiratory dysfunction) using the propensity matched dataset. An interrupted time-series (also known as segmented regression) analysis as described by Wagner will be conducted for each outcome to estimate the pre-intervention time trend, immediate impact of intervention (change-point), as well as reliably estimating the slope change after the intervention. All estimates of interest from these models will be summarized with p-values and 95% confidence intervals.

Statistical analyses will be performed using R V3.5.1 (Vienna, AU) using the "Match" package for propensity score matching and p-values <0.05 will be considered statistically significant.

Prospective analysis: The prospective analysis will largely follow a similar framework however we will focus on the primary and secondary outcomes as described above and will use a one year period prior to implementation as our baseline.

Power/Sample Size:

Sugammadex was introduced into clinical practice at UCLA in May of 2016, thus we have well more than one year of data prior to and after sugammadex introduction. As a result, the power analysis and sample size discussion is roughly the same for the retrospective and prospective portions of this study.

Over the previous one year period, approximately 6,5000 patients received general anesthesia with the use of either rocuronium or vecuronium. Given that our surgical volumes are stable we would expect the sample size for the prospective portion of our study to be roughly the same. The table below contains the risk stratification for this group.

To determine the study power, we analyzed the incidence of the primary and secondary outcomes for our historical population. Because there is no current pathway, we are unable to explicitly model the power

for pathway compliance, however the power for the primary outcome as well as secondary outcomes were calculated.

In order to determine our power for the study variables patients were separated into low, medium, and high-risk groups. Low risk patients were those who had no prior documentation of OSA or respiratory disease prior to surgery. Medium risk patients were those with either OSA or respiratory disease and high risk patients were those with both diseases. It is important to note that this classification is significantly simplified as compared to the analysis that will be performed for either the retrospective or prospective studies as it fails to account for key factors such as severity of illness. Nonetheless we believe that these simplifications have the effect of underestimating the potential power and thus the below serves as a conservative estimate.

Given 1 year of data, we observed an overall average PACU discharge time of 152.54 minutes (SD=623.86). With one year of post-data, we are adequately powered (90%) to pick up a reduction in PACU discharge time as small as 24.84 (two-sample t-test, alpha=0.05). Since the current difference in PACU discharge time between low and high risk groups is 67.52 (subtracting 216.62

149.10, see table), we feel the 24.84 minimally detectable difference gives us a great chance of detecting a meaningful difference.

Given 1 year of data (pre-period), we observed the rate of patients with any time SpO2<90% was 4.6% (574/12,467). With one year of post-data, we are adequately powered (90%) to pick up a reduction in this rate if it decreases to around 3.8% in the post (chi-square test, alpha=0.05). Since the current difference in patients with any time with SpO2<90% between low and high risk patients is 5.2% (subtracting 9.2%-4.0%), we feel the minimally detectable difference of 0.8% (4.6%-3.8%) is feasible.