STIM BOWEL FUNCTION: Sugammadex **To IM**prove **Bowel Function**

Protocol and Statistical Analysis Plan
July 23, 2020

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Full Title: An assessor-blinded, randomized, controlled, single center, parallel design trial with patient masking to compare early postoperative gastric emptying associated with rocuronium neuromuscular reversal with sugammadex versus neostigmine in adults undergoing colon and rectal surgery

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1. Protocol Title

An assessor-blinded, randomized, controlled, single center, parallel design trial with patient masking to compare early postoperative gastric emptying associated with rocuronium neuromuscular reversal with sugammadex versus neostigmine in adults undergoing colon and rectal surgery

2. Objectives

Primary Hypothesis: We hypothesize that compared to neostigmine and glycopyrrolate, reversal of rocuronium neuromuscular blockade with sugammadex will increase gastric emptying in patients undergoing colorectal surgery.

Primary Objective: To determine if a strategy of rocuronium neuromuscular blockade reversal with sugammadex will increase gastric emptying as assessed by the paracetamol absorption test, compared to neostigmine and glycopyrrolate.

Secondary Objectives:

1. To determine if a strategy of rocuronium neuromuscular blockade reversal with sugammadex will reduce time to first bowel movement, compared to neostigmine.
2. To determine if a strategy of rocuronium neuromuscular blockade reversal with sugammadex will reduce the proportion (percentage) of patients with a gastrointestinal complication (anastomotic leak, postoperative ileus, reoperation, or organ space infection), compared to neostigmine.
3. To determine if a strategy of rocuronium neuromuscular blockade reversal with sugammadex will reduce the time between administration of reversal agent to achievement of a train-of-four ratio > 0.9, compared to neostigmine.
4. To determine if a strategy of rocuronium neuromuscular blockade reversal with sugammadex will reduce Post Anesthesia Care Unit (PACU) phase 1 recovery time, compared to neostigmine.
5. To determine if a strategy of rocuronium neuromuscular blockade reversal with sugammadex will reduce hospital length of stay, compared to neostigmine.

3. Background

Colon and rectal surgery is associated with high cost, long length of stay, high postoperative surgical site infection rate, high incidence of postoperative nausea and vomiting, and a high rate of hospital readmission.[1-3] The 30-day mortality rate after open or laparoscopic surgery for colorectal cancer is high—in many studies around 3%.[1,4-6] A six year study of over 170,000 patients having colon and rectal resections for malignant and non-malignant disease found a 30-day mortality rate of 8.5%.[7] Return of bowel function is of utmost importance in avoiding patient discomfort, morbidity, and mortality after colorectal surgery. The incidence of postoperative ileus after colorectal surgery has been reported to be 10-25%.[3,8,9] Postoperative ileus is defined as intolerance of oral intake due to a lack of coordinated bowel motility.[10] Significant attention has been paid to the development of

guidelines and programs to reduce the incidence of postoperative ileus and accelerate return of bowel function after colorectal surgery.

The American Society of Colon and Rectal Surgeons (ASCRS) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) created an enhanced recovery after surgery (ERAS) protocol to promote the following outcomes in patients undergoing colorectal surgery: "freedom from nausea, freedom from pain at rest, early return of bowel function, improved wound healing, and early hospital discharge".[2] An intervention that facilitates faster postoperative gastric emptying may impact many of these outcomes; in particular, nausea may be reduced, constipation-associated pain at rest may decline, return of bowel function would be accelerated, and time to hospital discharge may be shortened. While administration of medications such as Alvimopan and adjustments in anesthetic technique (providing epidural analgesia, minimizing crystalloid administration, using multimodal analgesia) are recommended, sugammadex is not currently considered in the ERAS protocol.[2]

Neuromuscular paralysis is required for the duration of open and laparoscopic colorectal surgery to decrease patient movement, improve operating conditions, and at times facilitate ventilation. Neostigmine and glycopyrrolate are commonly used to reverse rocuronium neuromuscular blockade at the end of surgery. Both neostigmine and glycopyrrolate impact bowel function. Neostigmine promotes and glycopyrrolate slows gastrointestinal motility[11,12]. Co-administration of neostigmine and glycopyrrolate can have variable effects on return of bowel function after surgery. In general, administering a higher proportion of neostigmine than glycopyrrolate is associated with faster return of bowel function.[13] Unopposed cholinergic activity from neostigmine administration can cause morbidity including bradycardia, bronchoconstriction, hypotension, urinary incontinence, and increased salivary secretions.[11] Thus, the ratio of neostigmine to glycopyrrolate is relatively fixed and cannot be adjusted to promote desired gastrointestinal outcomes. Sugammadex does not bind to acetylcholine receptors on bowel and is presumed not to affect bowel function.

Some investigations into the contribution of sugammadex versus acetylcholinesterase inhibitors to recovery of bowel function have been completed. In retrospective studies, sugammadex administration has been associated with faster time to first bowel movement[14] and less ileus-related delays in hospital discharge[15]. Conversely, two randomized, controlled clinical trials found no difference in outcomes related to gastrointestinal motility including time to first flatus[16], time to first bowel movement[16], and incidence of postoperative ileus[17]. One randomized, controlled trial found a shorter time to first flatus, but no difference in time to first bowel movement.[18] Lastly, one study found a trend towards faster gastric emptying with sugammadex.[19] A limitation of the aforementioned prospective studies[16-19] is they include patients having surgery on their thyroid gland, gallbladder, and other intraabdominal organs. These surgeries lack bowel handling and anastomosis, which translates to less effect on postoperative bowel function. It is hypothesized that a randomized, controlled trial involving patients having colorectal surgery will find faster gastric emptying, less nausea, and less gastrointestinal complications (including ileus) when sugammadex is administered to reverse rocuronium neuromuscular blockade, compared to neostigmine.

The purpose of this study is to determine if administering sugammadex for reversal of neuromuscular blockade instead of neostigmine and glycopyrrolate, a strategy that avoids cholinergic effects on the bowel, is associated with faster gastric emptying, shorter time to first bowel movement, less post-

surgical gastrointestinal complications, faster time to achieve a TOFr > 0.9, shorter PACU phase 1 recovery, and shorter hospital length of stay. If sugammadex is shown to improve the aforementioned outcomes, an argument can be made that sugammadex should be considered for inclusion in the ERAS protocol for Colorectal surgery.

4. Study Design

Design: Assessor-blinded, randomized, controlled, single center, parallel design trial with patient masking

Intervention Arm: Sugammadex for reversal of rocuronium neuromuscular blockade will be administered at a dose of 2 mg/kg actual body weight once T2 has reappeared on the train-of-four, in accordance with product labeling.[1]

Control/Standard Arm: Neostigmine and glycopyrrolate will be administered in a dose and ratio consistent with product labeling and best practice[2-4] once T2 has reappeared on the train-of-four (i.e. 0.07 mg/kg neostigmine actual body weight to a maximum of 5 mg given concomitantly with 0.2 mg glycopyrrolate for every 1 mg neostigmine).

Randomization and Assignment: Patients will be randomly assigned to either the intervention (sugammadex) or control (neostigmine) arm. Before initiation of the clinical portion of the study, 120 opaque sealed envelopes will be prepared by a researcher not involved in patient recruitment or enrollment: 60 for the intervention arm and 60 for the control arm. These envelopes will be randomized without stratification via a computer-generated random allocation sequence and numbered in ascending order from 1 to 120. A block size of 6 will be used for random number generation to ensure balanced assignments over time. Patients enrolled in the study will be assigned to the next free envelope and given the corresponding treatment contained therein. All researchers involved in patient recruitment, allocation, and assessment will be kept blind to the allocation sequence.

Research Integrity: The study will be assessed for initial approval by the Institutional Review Board (IRB) at OHSU, Portland, OR, USA, and given a unique identifier for ongoing review.

5. Study Population

a. Number of Subjects

Study Size: 60 subjects will be enrolled in the intervention (sugammadex) arm and 60 patients will be enrolled in the control (neostigmine and glycopyrrolate) arm at OHSU.

b. Inclusion and Exclusion Criteria

Inclusion Criteria: Patients ≥ 18 years of age having colorectal surgery under general endotracheal anesthesia in the south operating rooms of Oregon Health & Science University (OHSU). The following are examples of common colorectal surgeries at OHSU that would be eligible for

inclusion: abdominal perineal resection, colostomy reversal, colostomy revision, ileostomy reversal, ileostomy revision, bowel resection, protocolectomy, and proctectomy.

Exclusion Criteria:

1. Prisoners
2. Pregnant women
3. Patients lacking capacity to consent
4. Patients with an allergy to a study drug
5. Patients with a medical contraindication to neuromuscular blockade
6. Stage IV renal disease or worse (eGFR < 30 ml/min)
7. Significant hepatic dysfunction (AST or ALT > twice the institutional normal)
8. Patients taking the selective estrogen receptor modulator toremifene

c. Vulnerable Populations

The following populations will be excluded from the study

- Prisoners
- Decisionally impaired adults
- Pregnant Women

d. Setting

Study Location: Single center study performed at OHSU in Portland, OR, USA in the South Operating Rooms (highest acuity operating rooms). Subjects will be enrolled in the preoperative area of the South Operating Room Suite. All study interventions will occur in the South Operating Room preoperative area, the operating rooms, or in the Post-Anesthesia Care Unit. Data collection will continue to occur throughout the subject's hospitalization.

e. Recruitment Methods

Patient Recruitment and Enrollment:

Patients will be identified by the research staff and the general surgery team via review of the electronic medical record as posted in EPIC (Verona, Wisconsin) as early as two months prior to a potential subject's scheduled surgery.

We will review all the inclusion/exclusion criteria as early as two months prior to a potential subject's scheduled surgery. If a potential subject has been identified as meeting all inclusion criteria and none of the exclusion criteria, an approved study staffer will call the subject, using an approved phone script (included in 'Consent Form and Recruitment Materials' section of application) to introduce the study.

If interested, the patient will receive a follow up email that includes the informed consent.

If the subject is amenable to the study, study staff will make arrangements to meet with the subject to provide formal consent materials and signature at their pre-op visit or day of surgery. If the subject is not interested in participating in the study, the inclusion/exclusion criteria and any other information related to this subject will be destroyed.

The study will be listed on ClinicalTrials.gov to provide subjects, family members, and the public background information on the study.

Other than posting this study on OHSU Study Participation Opportunities, we do not expect to create advertisements for the study.

There will be no payments to subjects, we do not have funds to offer subjects payment for participation in the study.

f. Consent Process

The consent process will take place in a private and confidential area. All subjects that are approached for recruitment will hear a description of the study, reasons for pursuing this research study, options for opting out the research protocol or not completing data collection, and potential risks, advantages, and disadvantages from participating. We will ask subjects to reiterate their understanding of how the study will affect their care and allow time for questions before collecting a signature for consent. Subjects that agree to participate in the study will be asked to sign a written informed consent that has been approved by our Institutional Review Board. An electronic copy of the signed consent will be scanned into the subject's medical records system. A copy of the signed consent, describing the research study and providing contact information for the principal investigators will be given to subject.

Dr. Sydney Rose will serve as medical monitor and will conduct periodic reviews to ensure that proper consent devoid of coercion is being collected as the study progresses. Dr. Rose is an anesthesiologist at OHSU and the Associate Chief of Quality and Safety for the Department of Anesthesiology. She has clinical trial experience. Dr. Rose is currently the PI for two clinical trials.

Non-English speaking subjects will be enrolled with the help of an interpreter for all telephone communications, in-person procedures including obtaining consent, and study follow up. The short consent form will be used.

6. Procedures Involved

This is an assessor-blinded, randomized, controlled, single center, parallel design trial with patient masking to compare early postoperative gastric emptying associated with rocuronium neuromuscular reversal with sugammadex and neostigmine at Oregon Health and Science University (Portland, OR).

<u>Recruitment, Randomization, and Blinding</u>:

Patients will be recruited at home or during presurgical clinic visits by research staff or primary surgeons up to 2 months prior to surgery. Enrollment and acquisition of written informed consent will occur on the morning of surgery in the preoperative bay. Once a study subject signs a consent form, a unique number corresponding to the opened opaque envelope will be assigned to that subject. This subject number will never be reused and will remain with the subject for the entirety of the study. No subject will ever be allowed to have more than one unique subject number. All patients undergoing colorectal surgery will have an equal probability of being approached for the study.

Patients will be randomly allocated to rocuronium neuromuscular block reversal with sugammadex or neostigmine based upon a computer-generated random allocation sequence with 1:1 assignment ratio. The allocation sequence will be created before study commencement by a member of the clinical research department not involved in recruitment, coordination, or data collection. Allocation will be concealed in sequentially numbered opaque envelopes. Anesthesia providers will be blinded until they are ready to prepare and administer reversal, typically when surgical closure begins. Study personnel involved in recruitment, consent, and outcomes assessment will be blinded to group allocation until study completion. Assessors will not have access to anesthesia records. Patients will also be masked.

Baseline Characteristics:

The following baseline patient characteristics will be obtained on the morning of surgery:

1. Age
2. Sex
3. Race
4. Weight
5. Height
6. Body Mass Index
7. American Society of Anesthesiologists classification
8. Tobacco use/smoking (current, past, never)
9. History of COPD or chronic lung disease
10. Diagnosis of obstructive sleep apnea
11. History of cardiovascular disease
12. Diabetic status (uncomplicated, end-organ dysfunction)
13. Diagnosis of gastroparesis
14. Cancer (metastatic, localized, none)
15. Impaired mobility
16. Current home opioid use
17. Creatinine
18. AST and ALT
19. Albumin

Intraoperative Management:

All patients will have standard ASA monitors plus five lead EKG applied. Additional monitoring will be left to the discretion of the anesthesia team directing patient care. Anesthesia will be induced with propofol and the TwitchView electromyograph will be placed after cleaning the patient's hand with an alcohol pad. First, the TwitchView electromyograph stimulating electrodes will be placed over the ulnar

nerve just proximal to the wrist crease. Next, the recording electrodes will be placed over the adductor pollicis muscle and the first dorsal interosseous muscle. The ground electrode will be placed over the index finger. The TwitchView electromyograph will then be calibrated followed by administration of rocuronium to facilitate intubation. Next, a nasogastric or orogastric tube will be inserted. The nasogastric or orogastric tube will be inserted until gastric contents or bile is achieved. If gastric contents or bile cannot be suctioned the surgical team will help guide the gastric tube to the correct location. Gastric tubes are commonly used during colorectal surgery. A large bore peripheral IV or arterial line will be inserted to provide safe patient care and facilitate blood sampling to measure plasma paracetamol concentrations after surgery.

Anesthesia will be maintained with inhalational agent. Rocuronium will be intermittently dosed to achieve the desired depth of neuromuscular block, as directed by the surgical team. Decisions on when to dose and what quantity of rocuronium should be dosed for maintenance of neuromuscular blockade will be left to the discretion of the anesthesia team in the operating room. The level of neuromuscular blockade will be monitored in the operating room with the TwitchView electromyograph via automatic train-of-four measurement every 20 seconds, which is the device default.

During surgical closure the opaque envelope containing patient allocation will be opened. The anesthesia provider will dispose of the allocation sequence into the sharps bin immediately after reading it. This will help ensure research coordinator masking when they enter the operating room. Neostigmine, glycopyrrolate, sugammadex and paracetamol will be obtained from the research pharmacy. Neostigmine, glycopyrrolate, and sugammadex will be delivered to the anesthesia provider in the original vials. Vials containing reversal agents will be immediately disposed of in the sharps bin after medications are drawn up. A 1 gram paracetamol per 200 ml sterile water solution will be created in the research pharmacy and dispensed to the anesthesia provider. Prior to administering neuromuscular block reversal paracetamol will be administered down the orogastric or nasogastric tube. The gastric tube will then be rinsed with 20 ml of water. Providers will be encouraged to administer paracetamol immediately before administering neuromuscular reversal. The gastric tube will be removed or left in situ, per the direction of the surgical team.

Providers will be told to make their best effort to reverse neuromuscular blockade at a train-of-four count of 2. Neuromuscular reversal with be administered in accordance with random assignment. Administration of sugammadex or neostigmine will occur into a fast flowing intravenous line that is running wide open. Sugammadex will be dosed at 2 mg/kg actual body weight, rounded to the nearest 10 mg. Neostigmine will be dosed at 0.07 mg/kg actual body weight (maximum of 5 mg), rounded to the nearest 0.1 mg. Glycopyrrolate will be co-administered in the neostigmine arm at a dose of 0.2 mg of glycopyrrolate per 1.0 mg of neostigmine. To maintain blinding, the study team will not be present in the operating room when anesthesia providers access the randomization assignment and administer reversal. Anesthesia providers will page the research coordinator immediately after neuromuscular reversal is administered. The page will cue the research coordinator to enter the operating room and inquire the time of reversal. The research coordinator will be trained not to walk into the anesthesia workspace so as not to inadvertently view the anesthesia record.

Train-of-four ratios will be saved in the TwitchView monitor for analysis at a later time to determine time to achieve train-of-four ratio ≥ 0.9. Three consecutive train-of-four ratios ≥ 0.9 will be required.

Postoperative Study Procedures:

Blood samples will be obtained at the following timepoints after reversal: 15 (T15), 30 (T30), 45 (T45), 60 (T60), 90 (T90), 120 (T120), and 150 (T150) minutes. Each sample will require a volume of 1-2 mL of blood. These will be stored on ice and delivered to the pharmacokinetics laboratory to determine plasma paracetamol concentrations.

A research coordinator at the patient's bedside in the PACU will assess for PACU phase 1 recovery time and monitor for the following adverse events:

1. Drug hypersensitivity reaction
2. Bronchospasm
3. Upper airway obstruction
4. Bradycardia
5. Tachycardia
6. Unremitting coughing
7. Treatment of nausea or vomiting
8. Dysgeusia (foul, salty, or metallic taste)

Thereafter, the study team will conduct in-person daily assessment to identify gastrointestinal complications (anastomotic leak, ileus, reoperation, or organ space infection), in hospital mortality, determine time to first bowel movement, and determine hospital length of stay.

A phone call and screen of the electronic medical record will be completed 30-60 days after hospital discharge to assess for gastrointestinal complications. A standard pro forma will be used for the daily in-person hospital assessment and the post-discharge phone call.

Electronic Medical Record Data Extraction:

The following variables will be extracted from the electronic medical record after patient discharge.

1. Categorized surgical procedure
2. Laparoscopic versus open procedure
3. Surgical wound classification (clean, clean-contaminated, contaminated, dirty or infected)
4. Cumulative rocuronium dose
5. Intraoperative opioid dose in parenteral morphine equivalents
6. Train-of-four count at time of reversal
7. Volume of crystalloid administered intraoperatively
8. Volume of blood transfused intraoperatively
9. Estimated blood loss
10. PACU opioid dose in parenteral morphine equivalents
11. Use of epidural for postoperative analgesia
12. Duration of anesthesia
13. Duration of surgery
14. Time from paracetamol administration to arrival to PACU
15. Time from reversal to arrival to PACU

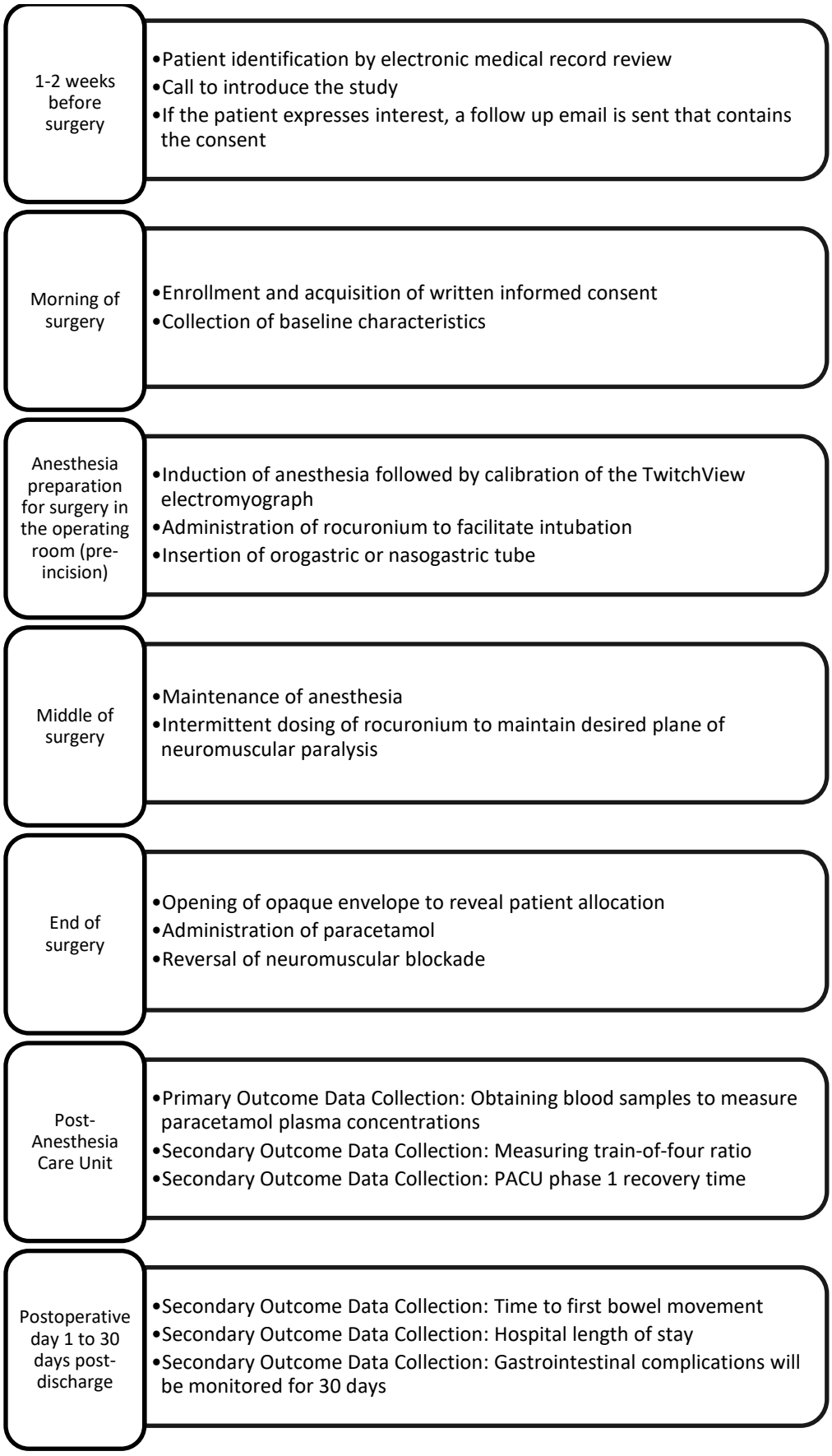
16. Presence of nasogastric tube in the PACU
17. Initial PACU glucose

Subjects enrolled that do not receive neuromuscular relaxant during surgery, for any reason, may be withdrawn from the study without their consent. In addition, a subject may be removed from the study if the investigator or funder stops the study, the subject's clinical status changes, or if the subject does not follow study instructions. In the event that such a situation occurs the subject would be informed at the earliest reasonable time.

The subject's status in the research project will show up clearly in their electronic medical record problem list, until the subject's participation is complete. A progress note will be placed in the subject's chart to allow other providers to easily contact study investigators.

Subjects that enroll in the study and then decide to withdraw before randomization and assignment occur will be excluded from further data collection and analysis.

An example of how the study would affect a single patient is shown in the diagram on the following page.


1-2 weeks before surgery
•Patient identification by electronic medical record review
•Call to introduce the study
•If the patient expresses interest, a follow up email is sent that contains the consent
Morning of surgery
•Enrollment and acquisition of written informed consent
•Collection of baseline characteristics
Anesthesia preparation for surgery in the operating room (pre-incision)
•Induction of anesthesia followed by calibration of the TwitchView electromyograph
•Administration of rocuronium to facilitate intubation
•Insertion of orogastric or nasogastric tube
Middle of surgery
•Maintenance of anesthesia
•Intermittent dosing of rocuronium to maintain desired plane of neuromuscular paralysis
End of surgery
•Opening of opaque envelope to reveal patient allocation
•Administration of paracetamol
•Reversal of neuromuscular blockade
Post-Anesthesia Care Unit
•Primary Outcome Data Collection: Obtaining blood samples to measure paracetamol plasma concentrations
•Secondary Outcome Data Collection: Measuring train-of-four ratio
•Secondary Outcome Data Collection: PACU phase 1 recovery time
Postoperative day 1 to 30 days post-discharge
•Secondary Outcome Data Collection: Time to first bowel movement
•Secondary Outcome Data Collection: Hospital length of stay
•Secondary Outcome Data Collection: Gastrointestinal complications will be monitored for 30 days

7. Data and Specimens

a. Handling of Data and Specimens

Study subjects will be assigned a unique study number after enrollment in the study. All data points, procedure related data, and electronic files for data analysis will be linked only to this unique study number. This study number will not contain any of the 18 HIPAA identifiers such as: geographic location, dates related to the individual, medical record number, account numbers, etc. The key linking study subjects to study code will be kept in a cloud location with special protection for confidential and restricted health information (the OHSU Box). Only the principal investigator and other study staff will have access to this key.

Data collected in the course of the study will be stored in Qualtrics on an OHSU server. Data will be managed by Praveen Tekkali, an analyst within the Anesthesiology and Perioperative Medicine Research Division. Again, this data tool will be only be made available to study personnel though a secure online log-in. Secure data will be stored in Qualtrics for indefinite use. Data in Qualtrics will be linked only to subject study code, not to any of the 18 HIPAA identifiers.

Any data that is shared will be transmitted in an encrypted manner over a secure network. Transmitted data will be labeled only with the study code, none of the 18 HIPAA identifiers. When data is transmitted, the transmitter (research personnel with access to Qualtrics) will be responsible for sending the data in a protected manner. Any person receiving data will then assume responsibility for patient confidentiality and data integrity.

Seven blood samples will be drawn after surgery. Samples will be kept on ice in a cooler in the PACU until all samples for a given subject have been collected. The cooler will be kept by the research coordinator at all times and will never be left unattended. Specimens will be labeled with subject study number and time the sample was drawn. For example, the blood sample for study subject #1 drawn 15 minutes after reversal will be labeled “1-T15”. Samples will then be prepared by centrifuge at 2000xg at 4C for 15 minutes. Samples will be stored in a freezer at -80C in the Anesthesia Research Refrigerator, Mackenzie Hall Room #2148. This is a secure locked area used for research. Samples will be stored in this room for 1 to 4 weeks. Samples will be batched and taken to the Bioanalytical Shared Resource/Pharmacokinetics Core at OHSU where they will be analyzed and discarded in accordance with blood waste guidelines in the Bioanalytical Shared Resource/Pharmacokinetics Core at OHSU. There will be no long term storing of plasma samples in the Bioanalytical Shared Resource/Pharmacokinetics Core.

b. Sharing of Results with Subjects

Study results will not be available to subjects at the time of participation. All subjects will be given the contact information of the principal investigator (Brandon Togioka) and told that they may contact him to obtain conglomerated de-identified data at the conclusion of the study. Patients will also be able to obtain a free copy of any published data should they indicate interest. The study will not generate any genetic information or imaging studies.

The laboratory data obtained will be plasma paracetamol concentrations. These values have not been linked to disease states and do not carry a risk of incidental findings. Individual laboratory results will not be shared with subjects or their healthcare providers.

c. Data and Specimen Banking

Data will be stored in Qualtrics for indefinite use. There is no plan to conduct additional research on this data set or to send data to a separate repository. Should an additional study be conceived IRB approval would be obtained before proceeding with data analysis. Requests for release of data would be addressed to the principal investigator. Release of data would need to be approved by the principal investigator, Director of Research, and Chair of the Department of Anesthesiology. No groups are excluded from requesting data access. All de-identified data within the Qualtrics database would be available for release. A data sharing agreement would be required before the principal investigator would allow researchers access to the data contained in Qualtrics.

8. Data Analysis

Data Analysis:

The database will be created and managed by Praveen Tekkali, a computer scientist within the Clinical Research Division of Anesthesiology and Perioperative Medicine. Dr. Yiyi Chen, an associate professor in biostatistics, will be responsible for performing the statistical analysis described herein. The research team led by Dr. Brandon Togioka will be responsible for interpreting the data.

Blinding of Data:

The statistician will be responsible for generating the random assignment list. Study subjects will be assigned a unique study number after enrollment. The key linking subject study numbers to the allocation sequence will be kept in an OHSU approved cloud location with special protection for confidential and restricted health information (the OHSU Box). The data manager, Praveen Tekkali, will guard this key. The outcome assessor will not be in the operating room when allocation is revealed or when neuromuscular reversal is administered. Variables that need to be retrieved from the electronic medical record will be pulled by the data manager to avoid unblinding the outcome assessor. After data collection is complete for the final patient the key linking the subject study numbers to the allocation sequence will be given to the statistician. At this point the remainder of the research team will be kept blinded in case data cleaning is necessary. For the purpose of the final analysis, the official clinical database will not be unblinded to the rest of the research team until medical/scientific review has been completed, protocol violators have been identified (if appropriate), data has been declared complete, and statistical analysis is finished.

Variables/Time Points of Interest

Primary Endpoint: **Gastric emptying to be assessed by the area under the paracetamol concentration versus time curve will be determined at 150 minutes by trapezoidal approximation**. In addition, the individual paracetamol plasma concentrations will be compared between study arms at the following timepoints after neuromuscular reversal: 15 (T15), 30 (T30), 45 (T45), 60 (T60), 90 (T90), 120 (T120), and 150 (T150) minutes.

The paracetamol absorption test is a validated test for assessment of gastric emptying that is more feasible in the perioperative setting than the gold standard of scintigraphy.[1-3] Scintigraphy is a test performed with nuclear medicine. It is a costly outpatient procedure that exposes patients to radiation. Paracetamol is poorly absorbed in the stomach, but is rapidly absorbed through the small intestine.[4] Thus, gastric emptying is the rate limiting step to allowing paracetamol to be absorbed into the blood stream.[4] Accordingly, higher plasma concentrations of paracetamol are associated with faster gastric emptying.

Please note, we realize Merck & Co. has experts in the field of pharmacokinetics. We would be more than happy to work with these experts to optimize our paracetamol absorption test.

Secondary Endpoint: **Time to first bowel movement**. This variable will be monitored on an ongoing daily basis until hospital discharge.

Secondary Endpoint: **The proportion (percentage) of patients with a gastrointestinal complication**. Gastrointestinal complications will include the following: anastomotic leak, postoperative ileus, reoperation, and organ space infection. National Surgical Quality Improvement Project definitions will be used.[5] Active monitoring for these outcomes will occur on an ongoing daily basis until hospital discharge. In addition, chart review and patient phone call will occur 30-60 days after discharge to assess for complications that occur after discharge.

1. Anastomotic leak will be defined as visualized leak of endoluminal contents through an anastomosis or presence of infection or abscess thought related to the anastomosis within 30 days of the index operation.
2. Postoperative ileus will be defined as prolonged NPO status or gastric tube for decompression for more than 3 postoperative days or reinserting a gastric tube or reinitiating NPO status at any time between postoperative day 4 and postoperative day 30.
3. Reoperation will include any surgery performed to correct a complication related to the index operation within 30 postoperative days.[6]
4. Organ space infection will include infections within 30 days of the index operation that involve a structure, other than the skin, that was manipulated.

Secondary Endpoint: **The time between injection of sugammadex or neostigmine and achievement of train-of-four ratio ≥ 0.9**. The TwitchView electromyograph will set to automatically check a train-of-four ratio every 20 seconds. These data points will be saved in the TwitchView monitor for download and analysis at a later time. A research coordinator in the PACU will turn off the TwitchView device once three consecutive ratios are ≥ 0.9. If a train-of-four ratio ≥ 0.9 is not achieved within 30 minutes after study drug injection the patient will be considered to have incomplete reversal and train-of-four counts will cease to be measured.

Secondary Endpoint: **Phase 1 PACU recovery time**. PACU phase 1 recovery time is defined as the time required to attain pain control and stable respiratory, hemodynamic, and neurologic status. This variable will be assessed by a research coordinator in the PACU on postoperative day zero.

Secondary Endpoint: **Hospital length of stay**. This variable will be monitored on an ongoing daily basis until hospital discharge.

Safety Endpoints:

1. **In hospital mortality** will be defined by a death in the hospital. This variable will be monitored on an ongoing daily basis until hospital discharge.
2. **Drug hypersensitivity reaction** will be defined by flushing, urticaria, new edema, sudden hypotension or tachycardia, or wheezing within 5 minutes of administration of study drug. This variable will be assessed by the research coordinator at the time the patient arrives to the PACU.
3. **Bronchospasm** will be defined by the need to administer a bronchodilator, such as albuterol, in the PACU. This variable will be assessed on an ongoing basis by the research coordinator in the PACU.
4. **Upper airway obstruction** will be defined by the requirement to place a nasal airway, or airway, or initiation of continuous positive airway pressure in the PACU. This variable will be assessed on an ongoing basis by the research coordinator in the PACU.
5. **Bradycardia** will be defined by a heart rate < 60 beats per minute at any time while the patient is in the PACU. This variable will be assessed on an ongoing basis by the research coordinator in the PACU.
6. **Tachycardia** will be defined by a heart rate > 100 beats per minute at any time while the patient is in the PACU. This variable will be assessed on an ongoing basis by the research coordinator in the PACU.
7. **Unremitting coughing** will be defined as ≥ 3 consecutive coughs at any time while the patient is in the PACU. This variable will be assessed on an ongoing basis by the research coordinator in the PACU.
8. **Nausea or vomiting** will be defined by nurse administration of an antiemetic or witnessed vomiting in the PACU. This variable will be assessed on an ongoing basis by the research coordinator in the PACU.
9. **Foul, salty or metallic taste** will be assessed by asking the patient if they have any unpleasant taste. This variable will be assessed on an ongoing basis by the research coordinator in the PACU.

Statistical Methods

Descriptive summaries will be presented as mean, standard deviation, median and range for continuous characteristics and frequencies and percentages for categorical characteristics, overall as well as by group.

All statistical analysis will use intent-to-treat patient population.

Primary analysis: Welch's t-test will be used to test for a treatment effect for the primary endpoint of area under the curve at 150 minutes. Log transformation will be applied to the AUC when necessary. The Welch's t-test will also be used to test for a treatment effect for paracetamol plasma concentration

at T15, T30, T45, T60, T90, T120, and T150. Mixed effect model will be used to compare the treatment effects over time (from T15 to T150) for the two groups.

Secondary analysis: Welch's t-test will be used to test for a treatment effect for the secondary endpoints time to first bowel movement, time to achieve a train-of-four ratio ≥ 0.9, PACU phase 1 recovery time, and hospital length of stay. The chi-square statistic or Fisher's exact test will be used to test for a treatment effect for postoperative gastrointestinal complications.

We will not conduct an interim analysis since we will need the full sample to evaluate efficacy. A two-sided alpha level of 5% will be required for statistical significance. The statistical software STATA (Stat Corporation, College Station, TX) will be used for analyses.

Multiplicity

This study consists of two treatment groups, no planned interim analysis, a single primary endpoint, and includes a statistical strategy in which a single pre-specified null hypothesis will be tested. Accordingly, adjustment for type I error is not required.

Power/Sample Size:

An abstract was published that compared sugammadex with neostigmine for the primary outcome of gastric emptying by paracetamol absorption.[7] The data generated from that abstract was used for sample size calculations. Assuming a pooled standard deviation of 140 and an area under the curve of 627 mcg*min/ml in the sugammadex group and 548 mcg*min/ml in the neostigmine group, the study requires a sample size of 50 in each group to achieve 80% power at 5% significance level using two-sided two-sample t-test. Ten subjects were added to each group to account for possible dropouts.

Timeline:

A review of colorectal surgeries at OHSU in the South Operating Rooms in 2019 found 179 surgeries. Our rate of enrollment in our last Merck sponsored sugammadex study was 56% (200/358). Assuming we have a similar enrollment rate we should be able to enroll 120 subjects in 18 months, with a projected enrollment of 1-2 patients per week.

9. Privacy, Confidentiality, and Data Security

The results of the study as well as all other information collected on the data collection sheet will be stored on site at OHSU in the office of the research coordinator. This office requires a key for entry and the corridor to the office requires a passcode for entry. The office is not shared with any other individuals. No protected health information or other data collected during the completion of this randomized controlled trial will be taken off campus. All data gathered for this study will be coded before any analysis or publication occurs.

This study number will not contain any of the 18 HIPAA identifiers such as: geographic location, dates related to the individual, medical record number, account numbers, etc. The key linking study subjects to study code will be kept in a cloud location with special protection for confidential and restricted health

information (the OHSU Box). Only the principal investigator and other study staff will have access to this key.

Data collected in the course of the study will be stored using OHSU's preferred secure database platform (Qualtrics). Again, this data tool will be only be made available to study personnel though a secure online log-in. Secure data will be stored in Qualtrics for indefinite use. Data in Qualtrics will be linked only to subject study code, not to any of the 18 HIPAA identifiers

In order to maintain patient privacy, data capture tools, study drug accountability records, study reports, and communications will identify the patient only by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authorities access to the patient's original medical records, including medical history, laboratory studies, and medication administrations, for verification of data gathered and to audit the data collection process. This information will be accessed for the duration of the research study, including the follow-up period, for the purpose of data reconciliation. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10. Provisions to Monitor the Data to Ensure the Safety of Subjects

DSMP submitted as a separate document.

11. Risks and Benefits

a. Risks to Subjects

As with all studies, breach of confidentiality is a common risk. In addition, there is the possibility of slightly increased anxiety on the day of surgery for patients approached for inclusion in the study. There is also likely to be a loss of free time in the preoperative area as consent will likely take 15 minutes to complete. TOF ratios will also be obtained in the Post-Anesthesia Care Unit (PACU), which is not currently standard of care at OHSU. This TOF ratio may result in a slight discomfort. Based upon our experience with our previous study involving sugammadex, patients do not remember having their TOF ratio measured. The TOF ratio will be measured while the patient is still under a significant depth of anesthesia. As data collection will continue to occur throughout the patient's hospitalization inconvenience is possible.

The orogastric or nasogastric tube is part of the standard anesthesia pathway for colorectal surgery. Accordingly, no additional risk is incurred by study participation. The decision regarding removing the gastric tube or leaving it in after surgery will be left to the discretion of the surgical team.

Large bore peripheral IV access and arterial line insertion are common procedures in the South Operating Rooms (High Risk Surgical Suite). For most patients having colorectal surgery in the South Operating Rooms the lines placed to ensure safe delivery of anesthetic care will suffice for postoperative blood sampling. If blood sampling cannot occur through the lines placed for surgery the least invasive method of obtaining blood samples will be used. This will typically mean the insertion of a new large bore peripheral IV.

Sugammadex is a novel method of reversing neuromuscular relaxant in the operating room approved by the FDA on December 15, 2015. There is a history of safe Sugammadex use in Europe since its initial approval by the European Union on July 29, 2008. As Sugammadex is a newer drug in the United States there is a possibility of unknown or understated adverse events associated with its use. To this extent adverse experience reporting will include monitoring for and publishing the occurrence of any of the following adverse events associated with sugammadex or neostigmine administration:

Adverse experience reporting will include monitoring for and publishing the occurrence of any of the following adverse events associated with sugammadex or neostigmine administration:

1. In hospital mortality
2. Drug hypersensitivity reaction defined by flushing, urticaria, new edema, sudden hypotension or tachycardia, or wheezing within 5 minutes of administration of neuromuscular blockade reversal
3. Bronchospasm in the PACU
4. Upper airway obstruction in the PACU
5. Bradycardia in the PACU
6. Tachycardia in the PACU
7. Unremitting coughing in the PACU
8. Nausea or vomiting in the PACU
9. Foul, salty, or metallic taste in the PACU

Participants will not incur any additional cost for participating in this study.

Sugammadex, acetaminophen, neostigmine, and glycopyrrolate are regularly handled by anesthesia providers. There is no additional risk to anesthesia providers that participate in this trial.

There is no risk to family of patients that participate in this trial.

b. Potential Benefits to Subjects

We are performing this study because the incidence of postoperative ileus after colorectal surgery has been reported to be 10-25%. Return of bowel function is of utmost importance in avoiding patient discomfort, morbidity, and mortality after colorectal surgery. Whether the study drug is better than the current standard of care at promoting return of bowel function is unknown. We anticipate that patients that receive Sugammadex will have faster gastric emptying, shorter phase 1 recovery length of stay, shorter length of hospitalization, and lower incidence of postoperative gastrointestinal complications including: anastomotic leak, postoperative ileus, reoperation, and organ space infection—compared to glycopyrrolate and neostigmine.

12. Drugs or Devices (delete if not applicable)

We request that sugammadex be provided by Merck & Co. as it was for our last trial. We request 80 vials of open label 200 mg/2 mL sugammadex solution for administration to 60 patients. We are requesting a surplus in case there are packaging or manufacturing defects or in case there are spills. In addition, some patients will require two vials because of their weight.

Vials of sugammadex can be sent to the research pharmacy at OHSU. The address and designated contact person can be shared at a future date. Individual vials can be sent, i.e. bulk supplies are not needed. The research pharmacy will be responsible for maintaining the inventory of sugammadex, safely and properly storing sugammadex in a secure location, and dispensing sugammadex solely for the purpose of completing the study protocol. Accurate records of sugammadex quantities drawn up, administered, wasted, and disposed of at the end of the study will be kept by the research pharmacy. Any unused sugammadex (either left over after patient administration or at the conclusion of the study) will be destroyed at OHSU pursuant to ICH/GCP guidelines, city of Portland regulations, state of Oregon regulations, federal policy, and OHSU institutional policy.

Blinding of sugammadex will not be necessary because the anesthesia provider will not be masked. The vials of sugammadex will be delivered unchanged to the anesthesia provider with the exception of a bright orange circular label that will identify the drug for research purposes only. The anesthesia provider will be responsible for checking, drawing up, labeling and administering sugammadex safely.

Paracetamol is available at our institution and we intend to purchase it for the study. The research pharmacy will similarly be responsible for maintaining paracetamol inventory, safely and properly storing paracetamol in a secure location, and dispensing paracetamol solely for the purpose of completing the study protocol. Accurate records of paracetamol quantities drawn up, administered, wasted, and disposed of at the end of the study will be kept by the research pharmacy. Any unused paracetamol (either left over after patient administration or at the conclusion of the study) will be destroyed at OHSU pursuant to ICH/GCP guidelines, city of Portland regulations, state of Oregon regulations, federal policy, and OHSU institutional policy.

Blinding of paracetamol will not be necessary. Paracetamol will be prepared for administration in the research pharmacy. One gram of paracetamol will be dissolved in 200 mL of water. This solution will be identified as a research drug by a bright orange circular label. The anesthesia provider will be responsible for checking, drawing up, labeling and administering paracetamol safely.

To avoid patient charges, sugammadex and paracetamol administered to study participants will be ordered and identified as a research medication in the electronic medical record.

The TwitchView electromyography is a device for measuring degree of neuromuscular blockade during surgery and in the acute postoperative period. The TwitchView allows for a more accurate assessment of neuromuscular function than the clinical observation of muscle function when using a peripheral nerve stimulator. A price quote has been obtained from the company that produces the TwitchView and

the sponsor has agreed to pay for the purchase of this equipment. The TwitchView is approved for clinical use in the operating room.

13. Study Duration

It is expected that this study can be completed within 30 months. The first 6 months would be used for the following: obtaining IRB approval, obtaining study drugs, setting up the research pharmacy account, developing the paracetamol assay and performing instrument validation, training research assistants on use of the TwitchView electromyograph, educating anesthesia providers, educating surgery providers, educating PACU nursing staff, and setting up a database. The next 18 months would be used for patient recruitment, patient enrollment, study implementation, data collection, and database creation. The final 6 months would be spent on data synthesis, statistical analysis, interpretation, writing, and revising the study for publication.

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