NCT03196167

Sugammadex and Decreased Time to Extubation

Study Protocol

6/19/2020

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2016-1)

Protocol Title: Efficacy and Safety of Sugammadex (2mg/kg) to shorten time-to-extubation among postoperative ICU patients following Aortic Valve Replacement, CABG surgery, or Aortic Valve Replacement with CABG surgery- a prospective randomized placebo- controlled trial.

Principal Investigator: Amit Bardia, M.D.

Protocol Version Number and/ or Date: Version5, June 1, 2020

(*If applicable*) **Clinicaltrials.gov Registration #: NCT03196167**

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   To demonstrate faster time to extubation after arrival in the cardiothoracic ICU in patients undergoing Aortic Valve Replacement (AVR), Coronary Artery Bypass Graft (CABG), or AVR/CABG combination surgery who receive study drug (Sugammadex 2mg/kg) as compared to placebo.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   Approximately 36 months
   It is estimated that 3 subjects will be randomized per week allowing for data collection to be completed in 2 years for study start-up, with an additional 12 months for data analysis.

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   Prolonged intubation after cardiac surgery continues to be a common clinical challenge and is associated with significant risks and costs[1-5]. Despite a Class I recommendation by the American College of Cardiology supporting care directed towards early postoperative extubation after low to medium risk Coronary Artery Bypass Grafting (CABG) surgeries[6]. A sizable proportion of patients continue to have a prolonged course of cardiothoracic intensive care unit (CTICU) intubation[1].

   Sugammadex, a gamma-cyclodextrin drug with a plasma elimination half-life of 2 hours. It rapidly reverses neuromuscular blockade by encapsulating the non-depolarizing aminosteroids agents[12]. Reversal of neuromuscular blockade with Sugammadex is not associated with cardiovascular effects that are commonly seen with traditional NMB reversal agents[13]. It can also reverse NMB more quickly and predictably than existing agents[14]. However, there have been sporadic reports of hypotension[15], anaphylaxis[16], elongated a PTT[17] with the use of Sugammadex. Additionally, although the FDA currently lists Sugammadex as indicated for reversal of neuromuscular blockade induced by rocuronium and vecuronium in adults undergoing surgery,[18] its use in the post cardiac surgery setting is limited due to lack of supportive data. In this context, the present study aims to test the effectiveness of a pragmatic and broadly applicable care pathway for shortening time to extubation among patients in the cardiothoracic ICU who have undergone AVR, CABG, or a combination AVR/CABG procedure. The FDA-approved package insert is attached as an appendix to this application.

4. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

   Anesthetic management per protocol: See also study flowchart attached

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1. For enrolled patients, anesthetic management will be left to the discretion of the attending anesthesiology provider with the exception that Rocuronium or Vecuronium (both SOC) will be used as the non-depolarizing NMB and that where sedation is desired.
2. Patients will be transferred to the CTICU intubated and on a propofol infusion and/or dexmedetomidine (Precedex) from the operating room. Both meds are used SOC.
3. Upon CTICU arrival, the patients surgeon and CTICU intensivist will determine if patient is able to proceed with fast-track extubation. Determination of continued eligibility based on the post-recruitment pre-randomization exclusion criteria will be determined by a member of the study team. Eligible patients will be randomized, investigational pharmacy will be contacted for study drug and within 30 minutes of the ICU admission, propofol will be discontinued. Precedex may be continued per clinical discretion.
4. The participant will be randomized to receive Sugammadex or placebo. The enrolled patients will be assigned to the study and control arms in a 1:1 ratio.
5. IDS will provide the Sugammadex (2mg/kg) vs. Placebo in a syringe. A qualitative train-of-four measurement will be obtained. The administration of the study drug and placebo compounds will be performed by CTICU nurses who will receive the drugs in a blinded fashion from the departmental research pharmacy. The study drug will be supplied by Merck.
6. The clinical care provider has the discretion to determine the appropriate ventilation settings on a case-by-case basis, in accordance with the suggestion that patients will be initiated on SIMV rate of 14 with 60% FiO_2, tidal volumes 8-10 ml/kg and PEEP of7.
7. Ten minutes after the drug administration, if the patient can lift their head and remains hemodynamically stable, the patient will be switched to CPAP mode of ventilation for 30 minutes. At the end of the CPAP trial tidal volumes, Rapid Shallow Breathing Index (RSBI) and ABG will be assessed. The patient will be extubated if he/she is not hypoxic/ hypercarbic, has RSBI<100 and has TV >300 cc.
8. If a patient fails the 30-minute CPAP criteria, the ICU intensivist will be immediately notified. Every attempt will be made to correct the underlying cause of CPAP failure, and a prompt reassessment will be made as deemed appropriate by the intensivist to reattempt CPAP versus continuing controlled mechanical ventilation.

Study participation will end when the patient is successfully extubated. AE assessment will be performed in the period immediately following extubation.

5. Genetic Testing N/A ☒

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.
   Patients scheduled to have Aortic Valve Replacement (AVR), Coronary Artery Bypass Graft (CABG), or AVR/CABG combination procedure.. CABG may be single or multi-vessel, and may be done on-pump or off-pump
7. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled

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in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion criteria for consent process:

All elective AVR, CABG cases,on-pump or off-pump, or combination of AVR/CABG surgery in adult patients with preoperative LVEF≥45% subject to the following exclusions:

Exclusions during consent process:

1. Emergency/unplanned cases
2. EF<45% or moderate /severe RV dysfunction
3. Estimated GFR < 30 mL/min
4. Patients on supplemental oxygen at baseline (home oxygen)
5. BMI>40 (calculated as the patient's weight in kilograms divided by the square of the patient's height in meters)
6. Patients with chronic opioid use preoperatively.
7. Patients with known neuromuscular disorders preoperatively.
8. Patients with a known sensitivity to Rocuronium or to Sugammadex.
9. Patients with known cognitivedeficitspreoperatively.
10. Patients < 21 years of age

Exclusions after recruitment but prior to randomization:

1. Postoperative Bleeding (chest tube output >100cc/hr)
2. Treatment of anaphylactoid reaction intraoperatively.
3. Patient's temperature<35.5 or >38.3 degree Celsius at the time of ICU arrival.
4. Determination that the patient will require prolonged mechanical ventilation possibly requiring muscle relaxation based on the intraoperative course and clinical judgment of the study PI or collaborating intensivists.
5. Intraoperative hypoxia or on arrival to the ICU. (Please see Study Flowchart).
6. Cardiac arrest
7. Sudden arrhythmia (Ventricular tachycardia runs/sudden bradycardia with improper pacemaker detection/function) precluding fast-track extubation protocol.
8. Need for two or more inotrope initiation precluding fast-track protocol. Only a single vasopressor/inotrope may be initiated without excluding the subject.
9. Postoperative ST changes.

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10.A positive standard of care pregnancy test during your pre-operative evaluation

9. How will **eligibility** be determined, and by whom?

Eligibility at pre-op and post-op will be based on protocol specific inclusion and exclusion criteria and will be determined by the PI or Sub-I's in collaboration with the ICU attending physician

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Sugammadex is generally safe and well tolerated. Potential risks associated with sugammadex are: hypersensitivity, including anaphylaxis/anaphylactic shock – previous trials suggest this risk is small. Cardiac arrhythmias including bradycardia & tachycardia where intervention is rare and responsive to usual treatment. Other reported risks include nausea, vomiting, constipation.

Bleeding was originally thought to be a side effect, but studies have since showed that Sugammadex falsely elevates the PTT without increasing bleeding risk. (see reference on last page.)

11. **Minimizing Risks:** Describe the way the above-mentioned risks will be minimized.

Patients will all be in a critical care environment and monitored very closely including: blood pressure, heart rate, and chest tube output will be tracked from arrival to the CTICU until extubation per ICU protocol. Subtle changes in the patient's hemodynamic status are easily seen and treated if necessary.

12. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan

1. Personnel responsible for the safety review and its frequency:

The principal investigator, with the DSMB will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews, which must be conducted at a minimum of every 3 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) and the DSMB will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or DSMB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. We do not view the risks associated with Sugammadex used as neuromuscular blocking reversal agent as minimal risk.
2. Given our experience with the administration of Sugammadex, an FDA approved medication, we do not view the proposed study as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Dr. Amit Bardia according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR

5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

Only the following adverse events will be tracked. These AE's will trigger an immediate DSMB review; any incidence of anaphylaxis; unexplained hypotension requiring initiation of pressors; cardiac pacing within 5 minutes of drug administration; tachycardia, bradycardia or onset of atrial fibrillation; or increases in chest tube output considered clinically significant by the critical care team. The DSMB will be notified within 2 business days of determination by telephone or email. A written report will be provided within 7 days of the determination. Any incidents meeting SAE criteria will be reported per the IRB reporting policy.

If the DSMB determines that study drug may be causing an increase in adverse events, the study will be suspended until the DSMB can fully review the events and make a recommendation in consultation with the Yale Human Investigations Committee. The local Merck research representative will also be notified about the events (within 2 business days in case of any serious adverse events). If the data monitoring board and/or IRB view that the study is unsafe, the study will be discontinued.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs only if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

☒ All Co-Investigators listed on the protocol.
☒ Study Grantor (Merck)
☒ Other Data Safety Monitoring Board (DSMB)
☒ Yale University IRB

The principal investigator Amit Bardia, MD will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

See also DSMB charter attached.

13. Statistical Considerations: Describe the statistical analyses that support the study design.

Variables/Time Points of Interest

The primary outcome is the time to extubation, which will be the duration from arrival to the ICU to the extubation time.

Proposed statistical test/analysis: Positively skewed variables will be log-transformed prior to hypothesis testing. For the primary outcome, a two-sided Student's t-test will be used to compare

the time to extubation between the two groups. If necessary, covariate adjustment will be made using the multiple linear regression analysis method. Differences between means and 95% confidence intervals will be estimated to describe the magnitude of intervention difference between the two groups. As part of sensitivity analyses, the time-to-extubation outcome will be also analyzed by the Cox regression model. To compare the categorical adverse events between two groups, chi-square test or Fisher's exact test will be used.

Missing Data: Prevention is the most obvious and effective manner to control bias and loss of power from missing data. Therefore, several strategies (e.g., timely data entry and daily missing data report) will be imposed to limit the likelihood that missing data will occur during this study. This protocol will follow the intention to treat principle, requiring follow-up of all subjects randomized regardless of the actual treatment received.

Power analysis: Our 'in-house' historical data (n = 73) showed that after excluding outliers greater than the 80th percentile, patients undergoing isolated CABG demonstrated a mean of 8.39 hours to extubation (SD 2.89). Although we anticipate a Hawthorne effect demonstrating reduced time to extubation in both the active and placebo arms of the present study, we have conservatively chosen to maintain power based on historical data. We therefore estimate that 45 subjects per group will give us 90% power to detect a clinically relevant effect size of 2-hours difference between active and placebo groups at an alpha value of 0.05 using a two-sided two-sample t-test. To allow for post consent, pre-randomization study drop out, we will aim to enroll a total of 110 (90 + 20 = 110) subjects.

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SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

1. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

B. DRUGS/BIOLOGICS ☐N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
2. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
3. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animalmodels.

BRIDION® (sugammadex) Injection, for intravenous use Initial U.S. Approval: 2015

3. **Source:** Identify the source of the drug or biologic to be used. Sugammadex 2 mg/kg

a) Is the drug provided free of charge tosubjects? ☒YES ☐NO
If yes, by whom? Merck Pharmaceuticials

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility andpyrogenicity.

Sugamadex is an FDA approved medication used to reverse neuromuscular blocking agents utilized for anesthesia. Sponsor will provide the medication and preparation & dispensing will be done by YNHH IDS.

Check applicable Investigational Drug Service utilized:

☒ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

5. Use of Placebo: ☐ Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
Currently there are no available therapies utilized for anesthesia reversal in this population. Standard of care is to let the NMB agent wear off.

b) State the maximum total length of time a participant may receive placebo while on the study.
Patient will only receive placebo once.

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
We don't expect any potential harm to come to participants associated with receiving placebo. The standard of care is to wait for anesthesia to wear off. Therefore, in absence of study drug treatment, the patient will be allowed to wake from anesthesia as he/she would if they weren't participating.

d) Describe the procedures that are in place to safeguard participants receiving placebo.
Patients will be monitored per standard of care in the CTICU until extubation, regardless of what treatment they are assigned.

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6. Continuation of Drug Therapy After Study Closure ☒Not applicable to this project

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

   Targeted for enrollment at Yale for this protocol: 110 enrolled with assumed randomization of 90 subjects.

   a. If this is a multi-site study, give the total number of subjects targeted across all sites:N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☐ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☒ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trialregistries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media(Twitter/Facebook):	
☒ Other: pre-admission testing, with subsequent chart review or referral by collaborating surgeons.		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Many subjects will be identified by screening pre-admission testing. Patients having planned AVR, CABG procedure (on-pump or off-pump), or a combination procedure of AVR/CABG will be approached by a member of the study team and the study opportunity will be presented. Additionally, the cardiac surgeons may refer patients for participation from their practices. Consent will be obtained at least 24 hours prior to surgery when possible. If potential subjects are missed in the pre-admission testing center, potential subjects may be contacted by phone by the clinical research nurse prior to the date of their surgery to determine if the subject is interested in learning of the study. If the potential subject is interested, the research nurse will provide a description of the study and a copy of the consent form via email, fax, or first-class mail based on the subject's preference. Once the subject has received and reviewed the consent, the clinical research nurse will answer any questions about participation by phone. Once the research nurse is satisfied that the potential subject understands the study and wishes to participate, the clinical research nurse will obtain a signed copy of the consent form from the subject using either email, fax or photograph of the entire document including their signature on the form and document it in the medical record. A copy of the signed form will be provided to the subject.

b. Describe how potential subjects are contacted.

Patients will be contacted in person in their surgeon's office or in the pre-admission testing area, by phone, or in their hospital room if they are hospitalized. When in-person contact is not possible, we will contact patients by phone.

c. Who is recruiting potential subjects?

All members of the study team

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☒ Yes, some of the subjects

☐ No

If yes, describe the nature of this relationship. The PI and members of the research team may be the treating anesthesiologist or the CTICU attending, providing care to the patient.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☒ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: Chart review will be utilized as a pre-screening tool before patients are approached regarding participation

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: Referral to the study team for potential participation will occur prior to consent being obtained.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

When the study team identifies, or is referred a patient who may be study eligible, the patient will be informed about the study. If the patient is interested they will have the opportunity to read the consent form and ask questions. The investigator or research staff will review the full Compound Authorization and Consent document with the subject discussing the purpose and scope of the study, explaining any risks and/or potential benefits, procedures associated with participation, economic considerations, confidentiality of the subject's information, and their ability to voluntarily participate and withdraw at any time during the study. will be explained in person. It will be explained to the subject that participation is completely voluntary and that they may withdraw at any time without penalty. Only after the patient has a thorough understanding of the study and what is being asked of them and after all their questions have been answered by a coordinator and an investigator, will they be asked to indicate a decision to participate by signing the consent form. Consent will be obtained at least 24 hours prior to surgery If potential subject are missed or not seen in-person in the Pre-Admission Testing Center, subjects may be contacted by phone by the clinical research nurse prior to the date of their surgery to determine if the subject is interested in learning of the study. If the potential subject is interested, the research nurse will provide a description of the study and a copy of the consent form via email, fax, or first-class mail based on the subject's preference. Once the subject has received and reviewed the consent, the clinical research nurse will answer any questions about participation by phone. Once the research nurse is satisfied that the potential subject understands the study and wishes to participate, the clinical research nurse will obtain a written consent via email, mail, fax or photograph of the entire document including the subject's signature on the consent form and document it in the medical record. A copy of the signed form will be provided to the subject.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
Once the explanation of the study is complete and the subject and/or surrogate verifies understanding, the study staff and/or investigators will ask questions of the participant and/or surrogate to elicit as to whether the participant understands the study and that participation is voluntary. Patients ability to sign consent on their own behalf may also be assessed by the surgeon and/or PAT staff if possible. If there are any doubts about the patient's cognition and surrogate will be approached to sign on the patient's behalf.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   If potential subjects are Non-English speaking a short form and translator will be used to obtain consent. If more than 2 participants are consented in any one language the full compound authorization and consent will be translated for future patients.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☒ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ Not Requesting any consent waivers

☒ Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☒ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☒ NO ☐ OR
- Does the research pose greater than minimal risk? YES ☐ NO ☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?

  ☐ Yes ***If you answered yes, stop. A waiver cannot begranted.***

  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Writehere*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? Name, MRN, DOB, historical & current; medical history and laboratory results, and study related assessments.

2. How will the research data be collected, recorded and stored?

   Data will be collected from the patient's medical record and kept in a paper file maintained by the study coordinator as source. Data will then be entered on a laptop computer in an OnCore database that is password protected and encrypted. Patient's will be assigned a study number in the research data base and the link will be maintained by the coordinator.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☐Secured Server

   ☒Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   Participants will be assigned a study number in the Oncore database and the link will be maintained by the coordinator. Paper charts will be kept in a locked file cabinet in the coordinators locked office.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Once the data analysis is complete and all publications have been finalized, the paper charts will be destroyed leaving only coded data.

6. If appropriate, has a Certificate of Confidentiality been obtained? *N/A*

SECTION V: POTENTIAL

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Potential benefits associated with participation include early extubation and participants may spend less time in a critical care setting. The risk of pneumonia may also be reduced. The study does have placebo, so participants may not experience any benefit.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   The alternative is to not participate and be extubated per the standard of care

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   There is no payment for participation

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   There is no cost to participate and study drug will be provided by Merck

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? Yes

   b. Where and from whom may treatment be obtained? If the patient is still hospitalized, care will be provided by the patient's treating physician or CTICU intensivist. If the patient has been discharged, while injuries or adverse events are not expected, care should be sought and the PI should be notified as soon as possible.

   c. Are there any limits to the treatment being provided? No

d. Who will pay for this treatment? Yale School of Medicine and Yale-New Haven Hospital will not provide funds for the treatment of research-related injury. If there are study related injuries treatment will be provided. The patient or their insurance carrier will be expected to pay the costs of this treatment.

e. How will the medical treatment be accessed by subjects? Care will be provided if necessary while the patient is hospitalized. If not in the hospital the patient should seek care as needed and notify the study team.

IMPORTANT

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?

Yes ☒ No ☐

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☒ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☒

c. Will a novel approach using existing equipment be applied? Yes ☐ No☒

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

Additional Reference: Bleeding risk

Rahe-Meyer N, Fennema H, Schulman S, Klimscha W, Przemeck M, Blobner M, Wulf H, Speek M, McCrary Sisk C, Williams-Herman D, Woo T, Szegedi A. Effect of reversal of neuromuscular blockade with sugammadex versus usual care on bleeding risk in a randomized study of surgical patients. Anesthesiology. 2014 Nov;121(5):969-77