Study Protocol and Statistical Analysis Plan

Protocol Title: Avoiding Neuromuscular Blockers to Reduce Complications
NCT Number: NCT03962725
Document Date: Jan 10, 2020

PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	Eliminating use of Non Depolarizing Neuromuscular Blocking Agents to Reduce Postoperative Pulmonary Complications: A multi-center, randomized control trial
Principal Investigator	Maximilian Schaefer, MD

B1. PURPOSE OF PROTOCOL

The purpose of the protocol is to test the hypothesis that elimination of the use of non-depolarizing neuromuscular blocking agents (NMBA) for maintenance of general anesthesia in patients at high risk of developing postoperative pulmonary complications (PPCs) undergoing non-cardiac operations is associated with reduced risk of PPCs.

Specific Aim 1: To test the primary hypothesis that avoidance of non-depolarizing NMBAs, as compared to standard care which includes the use of non-depolarizing NMBAs, is associated with a lower risk of a composite of PPCs (including respiratory failure, suspected respiratory infection, aspiration pneumonia or pneumonitis, atelectasis, bronchospasm and reintubation within 28 days of index operative procedure) and all cause in-hospital mortality both within 28 days of index operative procedure.

Specific Aim 2: To test the key-secondary hypothesis that avoidance of non-depolarizing NMBA, compared to standard care which includes the use of non-depolarizing NMBA, is associated with higher vasopressor equivalent dose, which may be the consequence of higher dosing of opioids and anesthetics. Further, we shall also evaluate the following secondary endpoints: duration of intraoperative hypotension (defined as mean arterial pressure <55mmHg), surgeon's assessment of surgical field, cost of anesthetic medications, time to PACU discharge readiness (interval between arrival and time when meeting PACU discharge criteria), rate of unplanned ICU admissions or return to operating room within 24 hours, hospital length of stay and 30-day readmission rates.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Importance:
The need for safe anesthesia practices is growing in parallel with global surgical volume[1]. Non-depolarizing NMBA are commonly used as part of 'balanced anesthesia techniques'. Though helpful in facilitating endotracheal intubation[2] and optimizing surgical conditions[3], their use has been strongly associated with higher risk of postoperative complications. Large retrospective registry studies have consistently shown non-depolarizing NMBA use to be associated with increased risk of PPCs[4,5], hospital length of stay, overall costs and 30 day unplanned readmission rates[6]. Overall, this may translate not only into significant *potentially avoidable* patient morbidity but also in substantial healthcare expenditure considering their widespread use.

Residual neuromuscular blockade and postoperative pulmonary complications: Incidence and proposed mechanisms
A recently published prospective cohort study from a US cohort estimated the incidence of residual neuromuscular blockade post-extubation at >60%[7]. Volunteer studies have demonstrated that even minimal residual neuromuscular blockade in the absence of anesthetics significantly impairs genioglossus muscle activity and thereby predisposes the patient to upper airway collapse[8]. Residual blockade leads to delayed initiation of swallowing, pharyngeal dysfunction, and incoordination thereby significantly increasing risk of aspiration risk[9]. Although these factors are recognized as the

primary drivers of increased risk of PPC in patients with residual neuromuscular blockade, other factors contribute as well. **Figure 1** summarizes the multiple pathophysiological mechanisms which increase the risk of adverse pulmonary complications in patients with residual paralysis.

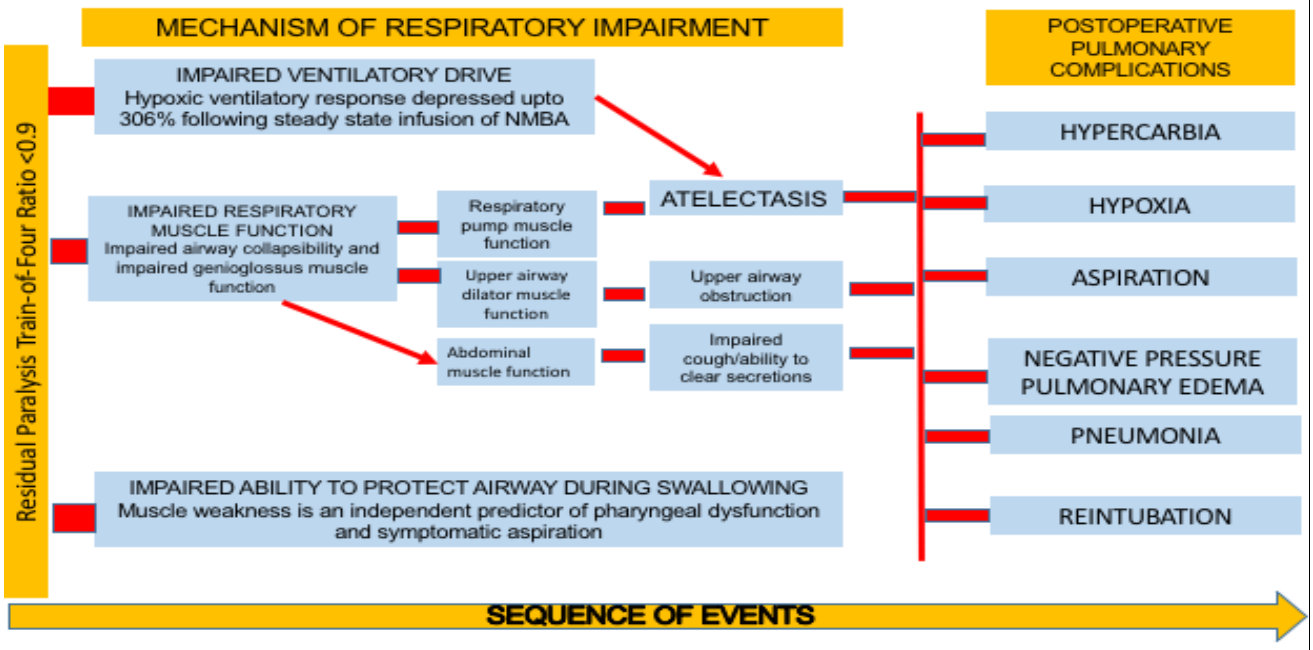

Figure 1: Pathophysiological mechanisms of residual neuromuscular blockade contributing to pulmonary complications. Impairment of the upper airway dilator muscle tone at even at minimal levels of residual neuromuscular blockade represents a key element that increases the vulnerability to aspiration, and negative pressure pulmonary edema. Avoidance of non-depolarizing NMBA may eliminate these mechanisms of postoperative respiratory complications.

Problems associated with reversal of neuromuscular blockade (NMB)

Counter-intuitively, observational studies indicate that antagonism of NMB with acetylcholinesterase inhibitors does not completely mitigate the risk of PPC, and can, paradoxically increase the risk of respiratory complications, which may be in part explained by depolarizing neuromuscular blockade [5,10,11]. In healthy volunteers, usual reversal dosage of neostigmine and glycopyrrolate given after complete recovery from NMB impairs upper airway dilator volume genioglossus muscle and diaphragmatic function, as well as skeletal muscle strength thereby predisposing patients to respiratory complications[12]. Although sugammadex is able to reverse various degrees of neuromuscular blockade quicker and has a better safety profile compared to neostigmine[13], its use does not completely mitigate the adverse effects of residual NMBA[4,10].

Inappropriate management of non-depolarizing neuromuscular blocking agents (NMBA)

Despite having been in clinical use over decades, significant practice variability exists among practitioners surrounding the use of NMBAs. Mirroring these observations, the recently published POPULAR study reported only about half of patients receiving NMBA were reversed, and a third were extubated at TOF-ratio<0.9 in contrast to established best practices[4]. Recent data show that the vast majority of anesthesiologists are *overconfident* in their ability to manage neuromuscular blockade, which likely contributes to the overwhelming belief that neuromuscular blockade could be managed intuitively without use of any objective neuromuscular monitoring[14]. This variability in provider practices is unsurprising, given that international societies are inconsistent in their guidelines. While few international societies advocate using some form of neuromuscular monitoring

when using non-depolarizing NMBA; only the Czech Society of Anesthesiologists explicitly recommends the use of quantitative monitoring and a TOF%>0.9 as adequate recovery. Notably the American Society of Anesthesiologists' guidelines on standards of basic anesthetic monitoring is silent on this topic [Accessed at asahq.org]. Thus, we expect that even during the proposed study, many anesthesia providers will not use NMBA appropriately - a trend noted in multiple observational and randomized control trials including our own work. We do not wish to standardize the use of NMBA in the control arm since we think both intrinsic side-effects as well as consequences of their inappropriate clinical use of NMBA affect patient safety.

Beneficial effects of NMBA

NMBA dose-dependently improve surgical conditions, and some authors conclude that deep NMB is associated with better operating conditions during specific types of surgery[3]. However, use of these agents is not an *absolute* requirement to achieve optimal conditions. In a double-blinded placebo-controlled RCT of patients undergoing prostatectomy under general anesthesia, only 24.5% of patients required a "rescue" NMBA in the placebo arm and good-to-excellent surgical conditions were achieved in 2/3 of patients in the placebo arm[15]. Inhaled anesthetics, opioids, and neuraxial analgesia can produce dose-dependent relaxation of skeletal muscles such that non-depolarizing NMBA may not be required to optimize surgical conditions. This protocol proposal also allows for rescue NMBA as needed.

In the intensive care unit, early use of NMBA in patients with severe ARDS has shown some benefits[16], probably by a reduction in patient-ventilator asynchrony. Although patient- ventilator dyssynchrony might be an issue in the operating rooms as well there are other medications which could be used to alleviate this issue successfully. The results of the recently concluded NIH-funded ROSE (Reevaluation of Systemic Early Neuromuscular Blockade) trial which our institution has contributed to, may even challenge the assumption of beneficial effects of NMBA.

Significance

More than 400 million people receive NMBAs annually, either in the operating theater or in the ICUs[5]. Use of non-depolarizing NMBAs during anesthesia is associated with an increased risk of clinically meaningful respiratory complications. Excellent surgical conditions can be achieved without the use of NMBA in patients undergoing a wide range of procedures including spine and prostate surgery[15,17]. Whether avoidance of non-depolarizing NMBA can mitigate the adverse postoperative risks associated with standard management of NMB is unclear in the absence of randomized controlled trials examining the consequences of use of non-depolarizing NMBA on PPC. Knowledge from this trial will help practitioners decide whether the elimination of NMBA may be a useful strategy to achieve better postoperative respiratory outcomes in patients at high risk of postoperative respiratory complications. The use or avoidance of non-depolarizing neuromuscular blockade agents to maintain general anesthesia and achieve optimal surgical conditions is accepted as the standard of care at both clinical centers regardless of patient participation in this study. Therefore, in addition to providing pilot data for a larger definitive trial, our results are likely to have an impact on the discussion of safety strategies to achieve optimal surgical conditions with and without NMBA.

Preliminary studies

Our study is aimed at patients with high pre-test probability of developing PPCs. In order to identify such patients preoperatively we developed a risk prediction score (**Table 1**) using data from all patients who underwent non-cardiac procedures under general anesthesia with endotracheal intubation at MGH and BIDMC between 2007-2015. 12.2% patients developed PPC (defined as a composite of reintubation within 7 days and respiratory failure, respiratory infection, bronchospasm, atelectasis, pleural effusion, aspiration pneumonitis, pneumothorax within 28 days). Our risk prediction-model which we developed using our published standards demonstrates good discrimination (AUROC of 0.84). We plan to use this prediction instrument along with expanded definition of high risk surgical services as defined by well validated SPORC score [18](vascular,

transplant, neurosurgery, thoracic, general and burn surgery) and physician review of electronic health records to determine "high risk surgery" to screen for eligibility. **Table 2** shows the predicted incidence of PPC in different risk subgroups of patients (MGH and BIDMC) in an 18-month period.

Risk Prediction Score	
High-risk surgery*	13
Inpatient surgery	11
Pneumonia within 1 month	8
ASA ≥ 3	3
Age ≥ 80	2
Duration of surgery > 3 hours	2
History of heart failure within 1 year	2
Alcohol abuse within 1 year	1
Home oxygen therapy	1
BMI < 18.5 kg/m^2	1
Chronic pulmonary disease within 1 year	1
Total points	44
**ENT, thoracic, vascular, transplant, neurosurgery, thoracic, general, and burn surgery*	

Estimated Risk of outcome	
Score Point Value	Probability of Outcome (%)
0	0.2
5	0.9
10	3.5
15	12.3
20	35.4
25	68.2
30	89.3
35	97.0
40	99.2
44	99.8

*The expanded definition of high risk surgical services as defined by SPORC score includes vascular, transplant, neurosurgery, thoracic, general and burn surgery.

Table 1: Risk prediction tool and estimated risk of outcomes. Logistic regression was used to build a model including all candidate predictors. Stepwise elimination was performed with a p= 0.01 for retaining in the model. Individual weighting values were determined by dividing the respective beta coefficient by the overall smallest beta coefficient of all predictor variables. Rounded to the nearest integer, the score point values were multiplied by the corresponding predictors, thus estimating the final prediction instrument.

Risk category for postoperative respiratory complications	**Predicted numbers of patients that can be recruited for the study within 18 months n (%)**
<10%	47,175 (78.2)
≥10% and <20%	8,519 (14.1)
≥20% and <30%	1,599 (2.6)
≥30% and <40%	288 (0.5)
≥40 and <50%	215 (0.4)
≥50%	2,567 (4.3)
Total number of patients	60,362 (100)

Table 2: Predicted number of patients in different risk categories that can be recruited within 18 months at MGH and BIDMC

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. STUDY DESIGN – OVERVIEW, METHODS, PROCEDURES

Experimental design and methods

Study Design
Pragmatic prospective randomized controlled assessor-blinded effect-size finding trial at two academic tertiary care hospitals: Beth Israel Deaconess Medical Center (BIDMC) and Massachusetts General Hospital (MGH).

Prior to randomization, if subjects are eligible on the basis of inclusion and exclusion criteria, informed consent will be obtained from the participants. Once informed consent is obtained, patients will be randomized in a 1:1-ratio to one of two study arms: standard care non-depolarizing NMBA use **(C)** versus avoidance of non-depolarizing NMBA **(NR)** by computer-generated variable block size random allocation stratified a) study site (MGH or BIDMC) and b) expected preoperative risk of PPC (<40% and >=40%) as predicted by expanded risk stratification tool as defined above (**Table 1**). Since blinding to use of NMBA is unfeasible, anesthesia team members would be aware of group assignment.

Intervention:

Pre- and intraoperative management plan would be left to the choice of the anesthetic team. The only protocolized restrictions in the two groups include the use or avoidance of non-depolarizing neuromuscular blocking agents. Normally, use or avoidance of non-depolarizing muscle relaxants for maintenance of general anesthesia is a clinical decision and either technique is accepted as standard of care at both participating centers. Choice and technique of induction and maintenance of anesthesia, use of vasopressors, perioperative antibiotics, analgesics/adjunct regional techniques, PONV prophylaxis, fluid and blood component therapy would be left at the discretion of the anesthesia team. Lung protective ventilatory strategies would be recommended. Use of monitors in addition to those recommended by standard ASA guidelines would be left to the discretion of the anesthesia team. Post anesthetic care and subsequent treatment would be left at the discretion of anesthesia and surgical teams per institutional protocols. Once a patient is enrolled into the study, the study team with review the protocol with the anesthesia care team before commencement of the surgery to address any questions or concerns.

Control Group (C): Use of neuromuscular monitoring would be allowed and management of neuromuscular blockade would be left at the discretion of the attending anesthesiologist. Endotracheal intubation would be facilitated by either Rocuronium (0.6-1mg kg^{-1}) or Succinylcholine (1-1.5mg kg^{-1}) and further dosing of Rocuronium would be left at the discretion of the anesthesia team members. Neuromuscular blockade would be reversed with either Sugammadex or Neostigmine (based on institutional availability) and trachea would be extubated once patient meets criteria per attending anesthesiologist.

No Relaxant Group (NR): Endotracheal intubation would be facilitated by Succinylcholine (1-1.5mg/kg) or Remifentanil (1-2mcg kg^{-1}) if Succinylcholine use is contraindicated. Use of both Succinylcholine and Remifentanil has been shown to provide excellent intubating conditions and is used commonly by practitioners. **No** non-depolarizing NMBA would be administered to the patients randomized to the **NR** group. Use of deeper plane of inhaled anesthetics or adjuncts (opioids, propofol, dexmedetomidine or ketamine) either as boluses or infusion would be recommended (**Figure 3**) in case of sustained high peak airway pressures (>35mm Hg), high intra-abdominal pressure, involuntary patient/diaphragmatic movement hindering surgical exposure and dissection. Choice and dose of adjunct/s to optimize operating conditions would be left to the discretion of the anesthesia team.

Use of rescue Neuromuscular blocking agents:
In case of *sustained inability* to obtain optimal surgical conditions despite optimal use of adjuncts, patients would be allowed a **rescue dose** of 0.2mg kg^{-1} of Rocuronium. Repeat dosages would be allowed only if sub-optimal operating conditions persist despite optimal use of adjunctive therapies.

In case of neuromuscular agent being used as rescue, NM blockade would be reversed at the conclusion of procedure with Sugammadex or Neostigmine (based on institutional availability) and trachea would be extubated once the patient meets subjective criterion including (TOF%>0.9) using quantitative monitoring.

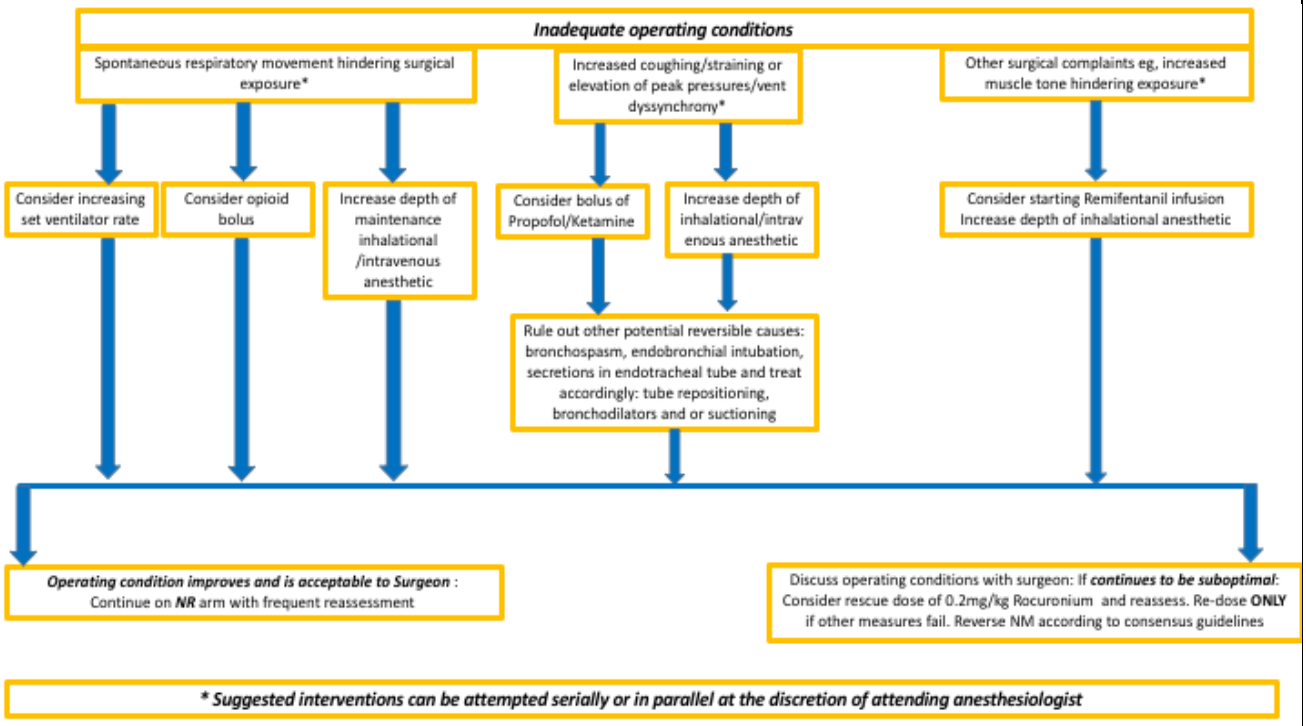

Figure 3: Suggested algorithm to mitigate inadequate operating conditions in **NR** arm

Study Endpoints:

1. Primary Endpoint: Composite of postoperative pulmonary complications (respiratory failure, suspected respiratory infection, aspiration pneumonia or pneumonitis, atelectasis, bronchospasm and reintubation) and all cause in-hospital mortality both within 28 days of index operative procedure
2. Secondary endpoint (safety):
    a. Vasopressor use between groups,
    b. Duration of intraoperative hypotension (defined as mean arterial pressure <55mmHg),
    c. Surgeon's assessment of surgical field.
3. Other end points:
    a. Time to post-anesthesia care unit (PACU) discharge readiness,
    b. Cost of anesthetic medication,
    c. Rate of unplanned ICU admission or return to operating room within 24 hours,
    d. Hospital length of stay
    e. 30-day readmission rates.

The following baseline variables will also be collected: Clinical and demographic variables will be collected including age, gender, body mass index, type and severity of chronic lung disease, ASA class, obstructive sleep apnea, use of CPAP/Bipap, smoking history, hypertension, coronary artery disease, heart failure, cerebrovascular accident or neurologic dysfunction, history of aspiration, use of home oxygen, chronic kidney disease, diabetes mellitus, Charlson comorbidity index and Procedural Severity Score. Additionally, to track other important intraoperative and postoperative

factors related to overall patient outcome and protocol adherence, we will record administrative, demographic, clinical and billing data including:

- Vital Signs
- Medications administered
- Ventilator settings
- Urine output
- End tidal carbon dioxide concentration
- Dead space ventilation
- Alveolar-Arterial oxygen gradient
- Blood transfusion history
- Length of operation
- Type of operation

Assessment of Primary Outcome:
Detection of postoperative pulmonary complications and in-hospital mortality would be achieved by close review of the patient's medical records during the hospital stay, for a maximum of 28 days. Study team members blinded to the treatment assignment will review clinician/ nursing/ respiratory therapy notes, laboratory/ imaging data and communicate with the clinical team as needed. Attending surgeons would be asked to rate overall operating conditions at the end of the procedure on a numerical scale modified from an earlier study.[15] To ensure blinding of assessors, printed anesthetic records will be placed in a sealed envelope and attached to the patient's chart after formal hand-off to nursing staff. Members of the clinical team will continue to have access to the anesthesia record through the electronic health record without restriction for the provision of clinical care.

Adverse Event Reporting:
We will assess for adverse events during the intraoperative period, as well as for the first 48 hours post-surgery.

Patients in this study are being randomized to anesthetic protocols that are both considered within the standard of care. We will adhere to the CCI post approval reporting requirements with regard to Adverse Events that are related, serious, and unexpected.

We will track the following pre-specified events as part of clinical outcome assessment. If any are deemed possibly related to study participation, they will be reported to the IRB in accordance with the reporting guidelines.

- Significant intraoperative hypoxemia
- Severe patient ventilator dyssynchrony
- Inability to ventilate
- Pneumothorax

Collaboration with MGH

This randomized control trial is planned in collaboration with MGH. We plan to recruit patients in parallel at the two institutions (BIDMC and MGH) and implement the study protocol after obtaining institutional approval. Dr Marcos Vidal Melo shall be the site PI at MGH and work in collaboration with Dr. Maximilian Schaefer, PI at BIDMC. A research coordinator credentialed at MGH will work under the guidance of Dr. Vidal Melo to follow study protocol at MGH. Similarly, a study coordinator will work with Dr. Maximilian Schaefer to follow protocol at BIDMC. Postoperative follow-up will be conducted by research staff credentialed at respective institutions through review of electronic medical records and in-person patient visits as appropriate for ascertaining components of PPC. Please see section B9 for more details on the collaboration.

1. STATISTICAL CONSIDERATIONS

a. ***Sample Size Justification:*** Assuming the incidence of PPC to be 40% and 15% in Groups C and NR, respectively, we estimated that we would need at least 50 patients in each group to achieve a two-sided α =0.05 and 80% power. Although the effect size in this assumption is high, if a difference of this magnitude is observed, the study will be well-powered. However, due to the scant knowledge about the directionality of the effect that we are exploring, observing even a smaller difference in this preliminary study will be useful in estimating a reliable effect size that can be used in designing a larger, more definitive study in the future. Results from our secondary endpoints will provide valuable exploratory data on the safety and efficacy of maintenance of general anesthesia without non-depolarizing NMBA.

b. ***Data Analysis:*** Descriptive statistics will be assessed and presented as mean(+/-SD), median(IQR) or frequencies and proportion depending on type and distribution. Differences between groups in continuous variables will be compared using parametric or non-parametric tests as appropriate. Categorical data including the primary outcome (composite of PPC and all cause 28 day in-hospital mortality) will be compared with Chi-square or Fisher's exact test as appropriate. Two-sided p-value of less than 0.05 will be considered significant for all analyses. Logistic regression will be used to assess the relationship between the composite outcome and use or avoidance of non-depolarizing NMBA. Data will be presented as odds ratio and 95% confidence intervals. Individual outcomes will be reported to demonstrate potential trends between the two groups. Continuous outcome variables will be compared between treatment groups using t-test or Wilcoxon rank sum test as appropriate. Exploratory sensitivity analyses will be conducted to analyze if treatment effects were moderated by study site, surgical site or preoperative risk score after adjusting for patient and procedural risk factors such as Charlson comorbidity index and Procedural Severity Score. Statistical consultation shall be provided by Dr. Timothy Houle, PhD at MGH. Statisticians will be blinded to group assignment.

Statistical analysis will be performed at BIDMC by experienced local study staff in collaboration with biostatisticians under the guidance of Dr. Timothy Houle (MGH). We shall establish a Data Use Agreement with MGH to facilitate exchange of de-identified study related data between the two study sites.

2. SUBJECT SELECTION

Inclusion criteria:

1. At least 18 years of age
2. Undergoing non-cardiac surgery under general anesthesia with an endotracheal tube
3. High estimated preoperative risk of PPC i.e. Score >=20 based on combination of expanded risk prediction score (including high risk services as determined by SPORC[18] scoring system) and physician review of electronic medical record (Table 1)

Exclusion criteria:

1. Emergency surgery
2. Ambulatory (outpatient) surgery
3. Scheduled for elective postoperative ventilation
4. Planned return to operating room within 7 days of index procedure
5. Exposure to general anesthesia within 7 days prior to planned procedure
6. Requirement mechanical ventilation at baseline (not including stable use of CPAP/BiPAP)
7. Pregnant patients: as detected by patient self-reporting or diagnosed by preoperative pregnancy testing according to institutional policies at BIDMC and MGH
8. Allergy to either non-depolarizing muscle relaxants or sugammadex

9. Clinician refusal
10. Prisoner

Women of childbearing potential:
Women of childbearing potential will be eligible for enrollment in this study. Preoperative pregnancy testing will take place according to the current BIDMC/MGH (as applicable) surgery and anesthesia guidelines. No additional serum or urine pregnancy test(s) will be performed for research purposes. Subjects will be excluded from participation if they are pregnant.

Gender and Racial Distribution of Subjects:

We anticipate that our study population will reflect the normal distribution of race and gender of patients presenting for non-cardiac surgeries at MGH and BIDMC

B4. POSSIBLE BENEFITS

As this is a pilot study, it is not possible to predict whether there will be direct benefit to the individual subject. However, based on our review of the literature, it seems plausible that elimination of the use of non-depolarizing muscle relaxants could result in lower incidence of postoperative pulmonary complications. These could potentially translate to lower morbidity, mortality, hospital length of stay and lower unplanned ICU admissions. Additionally, results from this trial would compare the relative safety and efficacy of these two techniques.

Data from this study can potentially provide pilot data to design a larger more definitive multicenter trial to assess whether the elimination of routine use of neuromuscular blockers can improve patient outcomes.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

The following includes descriptions of reasonably foreseeable risks or discomforts associated with participation in this study.

<u>Risks associated with elimination of muscle relaxation</u>
The primary risks associated with avoidance of neuromuscular blocking agents could in certain cases lead to patient-ventilator dyssynchrony, which might sometimes make ventilation difficult. Sometimes elimination of neuromuscular blocking agents may impede surgical exposure.

Neuromuscular blocking agents are not the sole agents which can provide muscle relaxation. There are reasonable alternatives which could be used to similar effect to facilitate ventilator synchrony and adequate surgical conditions. In case a subject experiences any of the risks above, or any unanticipated problems, the Principal Investigator or designated physician investigator will be available to coordinate care and counsel, as necessary. A suggested algorithm will be posted in the ORs to serve as a guide to trouble shooting these situations although the choice of agent and technique will be left eventually at the discretion of the anesthesia team members taking care of the patient. Although the avoidance of relaxants will be highly recommended and alternate pharmacologic measures suggested, the anesthesia team would be free to use relaxants as rescue in situations where suboptimal conditions persist despite the optimal use of other adjuncts. This mechanism is built into the protocol to mitigate any potential harm to the patients and ensure smooth conduct of the surgeries.

<u>Analysis of Risk/Benefit Ratio:</u>
There is a large body of literature suggesting that use of neuromuscular blocking agents is associated with overall worse postoperative outcomes. Most of this data comes from retrospective, observational study, but well-conducted randomized trials in this area are lacking. We believe that further research

including the current study is necessary to investigate whether the adverse effects associated with the widespread use of neuromuscular blockers can be mitigated by their avoidance. This study will also provide data about the relative safety and efficacy of the two proposed techniques of maintenance of general anesthesia. Detailed knowledge obtained from this trial will provide data for a larger multicenter trial to establish to relative safety of this agents and will also provide objective safety data to anesthesiologists to enable them to make informed choices surrounding the use of these commonly utilized agents. We believe that these potential benefits justify the mild-moderate risks associated with ventilator dyssynchrony or inadequate relaxation both of which could be mitigated by use of adjuncts other than neuromuscular blockers.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Members of the study team at BIDMC and MGH will screen operating room schedules, patient medical records for the presence of inclusion or exclusion criteria to determine eligibility for enrollment. A secure screening and enrollment log will be kept both at MGH and BIDMC. If a patient is deemed a potential candidate, they will be approached for informed consent.

Consent

Once a patient is found eligible, and after their clinical team has been notified, he or she will be approached by a member of the study team for informed consent. If the patient has questions or concerns that require physician input, the study team member (if not a licensed physician), will have immediate access to a study physician via page who will join the conversation. All consenting conversations will be documented in a memo to file or procedure note. This may occur in the surgeon's office, pre-anesthesia testing clinic, or in the preoperative holding area. All subjects will be consented with curtains drawn or the door closed, assuring patient privacy. The subjects will have the opportunity to ask any questions and are free to decline participation or withdraw consent at any time. Written informed consent will be obtained prior to surgery and any research procedures. Copies of the signed consent will be provided to the patient and filed in the medical record. The study team will work closely with the clinical providers throughout the study to ensure comfort with the protocol.

The study teams at both MGH and BIDMC undergo standardized, rigorous training regarding the informed consent process for research. The training is personally overseen by the Clinical Research Administrators at respective institutions and includes: didactic sessions, mandated attendance at CCI/HSPO seminars related to the informed consent process, shadowing of informed consent in a variety of contexts, trainee-led informed consent conversations with the aid of consenting checklists and accompanied by senior staff member and/or PI, robust feedback sessions, and clear communication when the team member is skilled enough to engage in informed consent discussions without direct supervision.

Subject Protection

Potential coercion of subjects will be avoided by obtaining informed consent by a physician or other members of the study team involved in the study and listed on the Research Staffing Form but not part of the anesthesia care team. Subjects or designated surrogated will be given enough time to review risks benefits, ask questions and decide whether they wish to participate in the study. Although patients of co-investigators may be approached for inclusion in this study, it will be clearly stated that the subjects' decision to participate or refrain from participation in the research study will not affect the performance or outcome of their upcoming surgery.

B7. STUDY LOCATION

Privacy

All study interactions will take place in private settings with curtains/doors closed so as to provide privacy and comfort for the subject. For patients being approached for informed consent, if they are uncomfortable answering questions regarding their medical history with someone other than a medical provider, an approved MD participating in the study will be contacted to conduct that portion.

Physical Setting
Enrollment will take place at BIDMC and MGH concurrently. Study procedures will take place in the operating rooms at BIDMC and MGH. Data collected will be housed on password-protected BIDMC and MGH network servers behind institutional firewalls. Paper records will be kept in locked filed cabinets/offices.

B8. DATA SECURITY

All study staff undergo formal training in proper research procedures, good clinical practice and application of HIPAA privacy laws.

Case report forms will be completed by study team members on site. All electronic files containing PHI will be stored on a secure research server behind the BIDMC and MGH institutional firewalls on password protected computers; paper files will be stored in locked cabinets at secure offices at BIDMC and MGH respectively. A crosswalk linking patient identifiers to study ID number will be maintained indefinitely by the PIs at both institutions behind institutional firewalls. Limited information will be retained on patients who are prescreened and do not qualify, or who are approached and declined, for the purposes of generating a CONSORT diagram at the conclusion of the trial.

De-identified data will be also be stored in REDCap a secure software managed separately at BIDMC and MGH which serves for data formatting. Medical Record Numbers, fiscal numbers, or patient names will not be entered into REDCap. Adverse events and protocol deviations logs will also be stored behind BIDMC/MGH firewalls respectively.

Study file transmission
When data is transmitted to the lead site (BIDMC) it will be done via secure entry in REDCap housed on BIDMC server according to the terms of DUA between MGH and BIDMC (to be executed). Data access groups for each study site ensure that site members only have access to data from their center. The coordinating site, BIDMC will have access to all data. A Data Use Agreement will be established between BIDMC and MGH to facilitate this exchange.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☒ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☒ Yes ☐ No

PI Communication: This bi-centric study is planned at MGH and BIDMC. The design of the study was discussed between site PIs. Regular meetings between responsible parties at each center and shared operations manuals will ensure consistency in methods between the study sites. At the regular meetings we will discuss further progress of the study and any other uncertainties or concerns that may require further clarification.

IRB Oversight: We plan to initiate a SMART IRB with the goal of MGH ceding review to the BIDMC IRB. The BIDMC PI and Study Coordinator will share all CCI communications and documents with the MGH study team in real time to ensure that the MGH group is working with current versions of

all documents. Regular teleconferences will be used to reinforce news of CCI communications, and in person meetings will be used to verify that current documents and procedures are in use. The eCRF will have fields for unanticipated problems (including AEs and non-compliance) which will trigger automatic emails to the BIDMC team to ensure fast communication. The BIDMC team will report events to the CCI in keeping with current CCI policies.

Data Considerations: Data collected by BIDMC researchers will be captured and saved on REDCap housed on secure BIDMC server. REDCap is a free secure HIPAA-compliant web-based application. Through this application coded data (not containing names, medical record numbers) will be shared by MGH (second study site) according to the terms of a Data Use Agreement. Data access groups for each study site ensure that site members only have access to data from their center. Select BIDMC team members will have access to all data for compliance review and data cleaning purposes.

The Principal Investigators at each centers (Drs. Schaefer and Vidal-Melo at BIDMC and MGH respectively) will retain the key assigned to their respective coded subjects. All subsequent reports of data from this study will be de-identified. Data monitoring and communication between study sites will be administered by BIDMC PI Dr. Schaefer and any appropriate designee(s).

B10 Dissemination of Research Results

Patients will be thanked for their time throughout the study. There is no plan to share the data at the conclusion of the trial. Because study results are likely to be published a few years after a given subject's participation, it is not feasible to send subjects follow-up with the published results. The study investigators are concerned that mailing the published manuscript and an additional thank-you note years after participation risks violating subject privacy, as mailing addresses are increasingly likely to change with passing time. It is out of the scope of this study to continue tracking mailing addresses after completion of enrollment since this is not a longitudinal study.

References

1. Rose J, Weiser TG, Hider P, Wilson L, Gruen RL, Bickler SW. Estimated need for surgery worldwide based on prevalence of diseases: a modelling strategy for the WHO Global Health Estimate. *Lancet Glob Health*. 2015;3 Suppl 2:S13-S20. doi:10.1016/S2214-109X(15)70087-2.

2. Lundstrøm LH, Duez CHV, Nørskov AK, et al. Effects of avoidance or use of neuromuscular blocking agents on outcomes in tracheal intubation: a Cochrane systematic review. *British Journal of Anaesthesia*. 2018;120(6):1381-1393. doi:10.1016/j.bja.2017.11.106.

3. Madsen MV, Staehr-Rye AK, Gätke MR, Claudius C. Neuromuscular blockade for optimising surgical conditions during abdominal and gynaecological surgery: a systematic review. *Acta Anaesthesiol Scand*. 2015;59(1):1-16. doi:10.1111/aas.12419.

4. Kirmeier E, Eriksson LI, Lewald H, et al. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. *Lancet Respir Med*. September 2018. doi:10.1016/S2213-2600(18)30294-7.

5. Grosse-Sundrup M, Henneman JP, Sandberg WS, et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. *BMJ*. 2012;345(oct15 5):e6329-e6329. doi:10.1136/bmj.e6329.

6. Thevathasan T, Shih SL, Safavi KC, et al. Association between intraoperative non-depolarising neuromuscular blocking agent dose and 30-day readmission after abdominal surgery. *British Journal of Anaesthesia*. 2017;119(4):595-605. doi:10.1093/bja/aex240.

7. Saager L, Maiese EM, Bash LD, et al. Incidence, risk factors, and consequences of residual neuromuscular block in the United States: The prospective, observational, multicenter RECITE-US study. *Journal of Clinical Anesthesia*. 2018;55:33-41. doi:10.1016/j.jclinane.2018.12.042.

8. Herbstreit F, Peters J, Eikermann M. Impaired upper airway integrity by residual neuromuscular blockade: increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure. *Anesthesiology*. 2009;110(6):1253-1260. doi:10.1097/ALN.0b013e31819faa71.

9. Sundman E, Witt H, Olsson R, Ekberg O, Kuylenstierna R, Eriksson LI. The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans: pharyngeal videoradiography and simultaneous manometry after atracurium. *Anesthesiology*. 2000;92(4):977-984.

10. Kotake Y, Ochiai R, Suzuki T, et al. Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. *Anesthesia & Analgesia*. 2013;117(2):345-351. doi:10.1213/ANE.0b013e3182999672.

11. McLean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M. Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications. *Anesthesiology*. 2015;122(6):1201-1213. doi:10.1097/ALN.0000000000000674.

12. Eikermann M, Fassbender P, Malhotra A, et al. Unwarranted administration of acetylcholinesterase inhibitors can impair genioglossus and diaphragm muscle function. *Anesthesiology*. 2007;107(4):621-629. doi:10.1097/01.anes.0000281928.88997.95.

13. Hristovska A-M, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. Cochrane Anaesthesia, Critical and Emergency Care Group, ed. *Cochrane Database Syst Rev*. 2017;8(5):CD012763. doi:10.1002/14651858.CD012763.

14. Naguib M, Brull SJ, Hunter JM, et al. Anesthesiologists' Overconfidence in Their Perceived Knowledge of Neuromuscular Monitoring and Its Relevance to All Aspects of Medical Practice: An International Survey. *Anesthesia & Analgesia*. August 2018. doi:10.1213/ANE.0000000000003714.

15. King M, Sujirattanawimol N, Danielson DR, Hall BA, Schroeder DR, Warner DO. Requirements for muscle relaxants during radical retropubic prostatectomy. *Anesthesiology*. 2000;93(6):1392-1397.

16. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-1116. doi:10.1056/NEJMoa1005372.

17. Li Y-L, Liu Y-L, Xu C-M, Lv X-H, Wan Z-H. The effects of neuromuscular blockade on operating conditions during general anesthesia for spinal surgery. *J Neurosurg Anesthesiol*. 2014;26(1):45-49. doi:10.1097/ANA.0b013e31829f3805.

18. Brueckmann B, Villa-Uribe JL, Bateman BT, et al. Development and validation of a score for prediction of postoperative respiratory complications. *Anesthesiology*. 2013;118(6):1276-1285. doi:10.1097/ALN.0b013e318293065c.