Intubating Conditions at Various Levels of Neuromuscular Blockade

NCT05620108

30Nov2022

Intubating Conditions at Various Levels of Neuromuscular Blockade

Regulatory Sponsor Principal Investigator: J. Ross Renew, MD

Funding Sponsor: Departmental Resources

Protocol Number: IRB # 22-009153

Initial version: [25Oct2022] Version **(1.0)**

Revision: [30Nov2022] Version (2.0)

Table of Contents

1 Protocol Approval Form

Protocol Number: 22-009153

Study Name:

Intubating Conditions at Various Levels of Neuromuscular Blockade

This protocol has been reviewed and approved by the following:

30 Nov 2022

J. Ross Renew, MD
Principal Investigator

Date

2 List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
cMAPs	Compound Muscle Action Potentials
CRF	Case Report Form
CTSA	Center for Translational Science Activities
DSMB	Data and Safety Monitoring Board
EHR	Electronic Health Record
EMG	Electromyography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICU	Intensive Care Unit
IRB	Institutional Review Board
MAC	Minimum Alveolar Concentration
MMG	Mechanomyography
NMBA	Neuromuscular Blocking Agent
Non-UPIRTSO	Non-Unanticipated Problems Involving Risk to Subjects or Others
PACU	Post Anesthesia Care Unit
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SGX	Sugammadex
SOP	Standard Operating Procedure
T_1	The first twitch of train-of-four stimulation
T_c	The amplitude of the baseline first twitch of train-of-four stimulation
TOF	Train-of-four
TOFC	Train-of-four count
TOFR	Train-of-four ratio
UPIRTSO	Unanticipated Problems Involving Risk to Subjects or Others

3 Study Summary

Title	Intubating Conditions at Various Levels of Neuromuscular Blockade
Running Title	Intubating Conditions
Phase	N/A
Methodology	Randomized, Open-Label
Overall Study Duration	12 months
Subject Participation Duration	15 minutes
Single or Multi-Site	Single site
Objectives	The primary aim of this study is to compare intubating conditions at varying levels of rocuronium-induced neuromuscular blockade
Number of Subjects	170
Diagnosis and Main Inclusion Criteria	Patients undergoing elective surgery and requiring administration of neuromuscular blocking agents prior to endotracheal intubation intraoperatively.

4 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

4.1 Abstract

Neuromuscular blocking agents (NMBAs) are a commonly utilized class of medications in the perioperative setting that can help facilitate endotracheal intubation, optimize surgical conditions, and assist with mechanical ventilation. Experts recommend the use of quantitative (or objective) neuromuscular monitors whenever NMBAs are utilized because these devices are the only method for reliably determining adequate neuromuscular paralysis and recovery of neuromuscular function. Unfortunately, several barriers exist that have prevented the widespread application of these devices, and many practitioners are still using qualitative (subjective) methods (i.e., use a peripheral nerve stimulator) as an assessment of neuromuscular blockade despite the lack of accuracy of subjective methods and the well-described morbidity and mortality associated with residual blockade. Objective monitors may also prove useful during the onset of NMB and provide useful information about when optimal intubation conditions have been reached.

The primary aim of this study is to compare intubating conditions at varying levels of rocuronium-induced neuromuscular blockade.

The TetraGraph (Senzime AB, Uppsala, Sweden) is an FDA-approved standalone EMG-based quantitative monitor that measures electrical activity within the muscle following peripheral nerve stimulation and is unaffected by involuntary patient motion or restricted muscle movements from surgical positioning. Following standard of care administration of propofol between 1 and 1.5 mg/kg and lidocaine between0.5 and1 mg/kg intravenously (IV) for induction of general anesthesia, the TetraGraph neuromuscular monitor will be calibrated, following which rocuronium at 0.6 mg/kg will be administered. Intubation will commence based on the one of two triggers based on randomization has been reached. One group will be intubated once the train-of-four count (TOFC) reaches 1 and the other when 2 minutes have passed. The time to intubation will be recorded and the intubating health care clinician will be surveyed about intubation conditions that includes variables such as: ease of laryngoscopy (jaw relaxation), vocal cord position and movement, airway reaction (coughing) and movement of the limbs (Table 17.2) The assessment will be done using video laryngoscopy display at the time of intubation.

4.2 Background

Neuromuscular blocking agents (NMBAs) are a class of medications routinely used during anesthesia to facilitate endotracheal intubation (1) and improve conditions for optimal surgery (2). However, these medications are also associated with respiratory complications in the early

postoperative period due to residual neuromuscular blockade (RNMB) (3-5). Even when neuromuscular blockade is reversed in the operating room, postoperative residual weakness continues to be a common problem in the post-anesthesia care unit (PACU), and a significant number of patients continue to arrive in the PACU with objective evidence of residual neuromuscular blockade (6, 7). While not every patient with residual weakness develops a postoperative complication, many can develop avoidable critical respiratory events (8, 9). Furthermore, special populations such as the elderly are at particular risk for developing complications related to postoperative residual weakness (10). The use of quantitative monitoring has been shown to reliably reduce the incidence of postoperative residual weakness and the ensuing complications (11-13).

Quantitative neuromuscular monitoring devices objectively measure residual weakness and display the results numerically. This is traditionally accomplished by performing a train-of-four (TOF) stimulation at the ulnar nerve and measuring the response of the adductor pollicis muscle. The degree of muscle weakness is determined by calculating the TOF ratio, which consists of the ratio of the fourth muscle contraction to the first. Adequate recovery that excludes clinically significant weakness from neuromuscular blockade is defined as a TOF ratio ≥ 0.9, a measurement that can be determined reliably only with a quantitative monitor (14, 15). With an abundance of literature supporting the use of objective neuromuscular monitors, a panel of experts recently recommended the universal adoption of such devices whenever NMBA are utilized (16) however, quantitative monitors can be expensive and require additional training.

Electromyography (EMG) is a type of quantitative monitor that measure electrical activity, termed compound muscle action potentials (cMAPs) following nerve stimulation (typically at the adductor pollicis muscle after ulnar nerve stimulation) (17). As EMG measures cMAPs and does not require freely moving thumbs for accurate measurements, many experts have referred to this monitoring modality as the “new gold standard”. TetraGraph (Senzime AB, Uppsala, Sweden) is a standalone EMG-based device that is FDA-approved.

Many clinicians default to the suboptimal practice of subjective monitoring (18, 19), which refers to visual or tactile evaluation of the train-of-four (TOF) in response to neurostimulation provided by peripheral nerve stimulation. However, subjective evaluation may provide inaccurate information and assessment of full recovery compared to objective evaluation (20, 21). A consensus statement by the international panel of experts in neuromuscular blockade issued in 2018 state that subjective evaluation is not predictive of adequate neuromuscular recovery and is not sensitive to the presence of residual weakness. They state that their use should be abandoned in favor of objective monitoring, because after the TOFR recovers to >0.40, anesthesia providers can no longer detect the presence of fade by subjective evaluation and they may assume a complete recovery from neuromuscular blockade, despite the presence of minimal levels of NMB (16). It is worth highlighting that after tracheal extubation, even minimal degrees of residual block is associated with impaired function of respiratory and pharyngeal muscles, upper airway obstruction (22), hypoxemia (23), and awareness during anesthesia (24)

Utilizing recommendations from the Good Clinical Practice (GCP) Guidelines for monitoring of neuromuscular function (25), we will compare intubation conditions at varying levels of

neuromuscular blockade utilizing EMG. Currently, our practice has significant heterogeneity in determining when the appropriate time to perform endotracheal intubation following induction of anesthesia. Following induction with propofol, rocuronium is administered and patients can have significantly varied response to this medication. Most providers wait approximately 2 minutes before intubating the patient's trachea. Given this drug's variable pharmacokinetics, quantitative monitoring may be used to objectively determine when optimal intubating conditions have been achieved. While use of these devices during induction of anesthesia represents best practice, it is rarely performed. In fact, it is very common to observe endotracheal intubation in a patient that has not yet had complete onset of neuromuscular blockade as evidenced by coughing or movement of the limbs following intubation. Further complicating the matter is that there is no method for objectively measuring the muscle groups that are important during intubation (oropharyngeal adductors and the diaphragm) and clinicians must make inferences about these muscle groups based on other muscle groups (adductor pollicis). Having a better understanding of the correlation between objective measurements at the hand and intubating conditions can provide anesthesia providers important information regarding the timing of endotracheal intubation.

4.3 Risks and Benefits

- Utilization of quantitative neuromuscular monitors is currently standard of care at Mayo Clinic. However, most providers place these devices after induction of anesthesia. Placing them prior to induction ensures they are working appropriately throughout the perioperative experience.
- Intubating the trachea at a TOFC=1 could result in conditions that suboptimal with movement of the vocal cords. However, the current standard of care involves intubating once about two minutes has elapsed and movement of the vocal cords is commonly seen. Whether the TOFC=1 or two minutes has elapsed, endotracheal intubation carries the risk of damage to the vocal cords. Utilization of the TOFC=1 represents a potential benefit to the patient as providers will have to use a quantitative neuromuscular monitor to determine intubation timing, rather than just intubating based on unclear, subjective endpoints.

5 Study Objectives

Primary Objective
Compare intubating conditions when patients are intubated at 2 different endpoints: TOFC=1 or 2 minutes after administration of rocuronium at 0.6 mg/kg (usual current clinical routine).

Secondary Objective
Correlate the ratio of the amplitude of the first twitch and control twitch (T_1/T_c) to intubating conditions.

6 Study Design

6.1 General Description

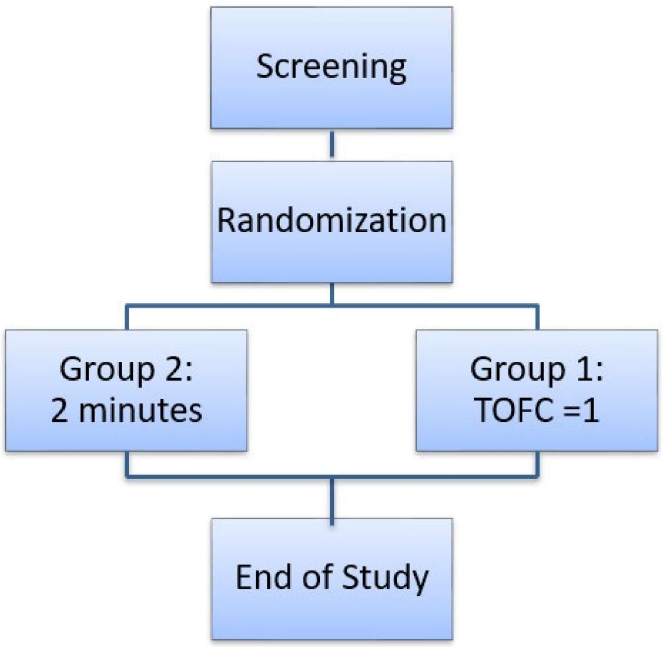
This unblinded, single center, prospective, randomized, study will involve 170 patients undergoing surgical procedure that involved administration of neuromuscular blockade agents intraoperatively in elective surgical procedures.

6.2 Number of Subjects

170

6.3 Duration of Participation

15 min at the start of the operation



6.4 Primary Study Endpoints

Compare intubating conditions when patients are intubated at 2 different endpoints: TOFC=1; or 2 minutes after rocuronium at 0.6 mg/kg. The assessment of the intubating conditions will be evaluated by the healthcare providers using a scale (Table 17.1) that includes 4 variables (ease of laryngoscopy, vocal cord position, and reaction to tracheal tube insertion with 3 response options

per each evaluation. The composite score (1-3) will be compared between groups, with the lowest total score of 3 correlating with optimal intubating conditions and the highest score of 9 representing the worse possible intubating conditions. The scale has been validated previously. (25)

6.5 Secondary Study Endpoints

The secondary endpoint is to evaluate intubating conditions as a function of the amplitude of the first twitch and control twitch (T_1/T_c).

6.6 Identification of Source Data

The study data points will be recorded on the developed Case Report Forms (CRFs) by the study team members. In addition to the data collected intraoperatively, several intraoperative characteristics will also be extracted from the medical record (Table 17.2).

7 Subject Selection Enrollment and Withdrawal

7.1 Inclusion Criteria

- Age > or = 18 years old
- Patients willing to participate and provide an informed consent
- Patients undergoing elective surgical procedures that require use of NMBA agents (rocuronium) administered intraoperatively.

7.2 Exclusion Criteria

- Patients with disorders, such as stroke, carpal tunnel syndrome, broken wrist with nerve damage, Dupuytren contracture, or any similar wrist injury.
- Patients with systemic neuromuscular diseases such as myasthenia gravis.
- Patients with significant organ dysfunction that can significantly affect pharmacokinetics of neuromuscular blocking and reversal agents, i.e., severe renal impairment or end-stage liver disease.
- Patients having surgery that would involve prepping the arm into the sterile field.
- Patients receiving a rapid sequence induction.

7.3 Subject Recruitment, Enrollment and Screening

On a daily basis, there are over 70 elective surgical cases performed at Mayo Clinic in Florida and thus no difficulties in accrual are anticipated based on historical volumes. We will target at least 10 participants per week to complete this study. The initial accrual period will last at least 3

months followed by interim analysis and additional time for accrual will be determined to meet the target. Patients will be provided with a Research Participant Consent and Privacy Authorization Form describing the study devices, protocol, inclusion and exclusion criteria, as well as risks and benefits of participation.

7.4 Early Withdrawal of Subjects

7.4.1 When and How to Withdraw Subjects

Patients are free to withdraw at any time and for whatever reason. If patient withdraws consent prior to arrival to operating room, the study data will not be collected. If patient withdraws consent after study data was already completed, the participant will need to provide instructions to the study team to remove his/her data from the data set. Pre-specified reasons for discontinuing include, but are not limited to, the following:

- Patient Request: Patient decided that he/she did not want to continue (for any reason)
- Adverse Event: Patient experienced a related or unrelated event that would interfere with the study objectives/evaluation
- Inclusion/Exclusion Discrepancy/Violation: Patient should not have been enrolled
- Other: Any other reason

7.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a Participant withdraws from the study, no additional attempts will be made to contact the Participant.

8 Study Procedures

8.1 Visit 1 (Screening and Enrollment up to the day of surgery)

- Review of medical record
- Informed Consent - Patients will be identified during their preoperative appointment and introduced to a study; they will be provided with a copy of the consent document and information about the study. The consenting will take place after additional discussion on the day of surgery.

8.2 Visit 2 (Randomization and Treatment – day of surgery)

- Induction of anesthesia is standardized to utilize lidocaine dose between 0.5 and 1 mg/kg, propofol between 1and 1.5 mg/kg, and rocuronium at 0.6 mg/kg. Anesthesia will be maintained with sevoflurane at 1 minimum alveolar concentration (MAC) through the

induction and intubation sequence. Following induction but prior to rocuronium administration, TetraGraph will be calibrated, and the supramaximal current will be obtained as per standard of care practice.

- Prior to induction of anesthesia, the TetraGraph will be placed on the same arm as the IV catheter over the ulnar nerve and the thumb to measure the response of adductor pollicis nerve.
- Randomization will be performed utilizing REDCap and patients will be assigned to be intubated at TOFC=1 or 2 minutes after rocuronium administration.
- After NMBA administration, sets of measurements will be taken every 20 sec until the desired level of neuromuscular blockade has been reached or 2 minutes has passed since rocuronium administration, depending on the group. Once the level of blockade has been achieved or the appropriate time has lapsed, anesthesia providers will intubate the patient using video laryngoscopy.
- If the anesthesia team finds the intubating conditions to be unacceptable, bag mask ventilation will be continued until the anesthesiologists deems it appropriate to attempt laryngoscopy as per standard of care.
- Following intubation, perioperative care will be at the discretion of the anesthesiologist.
- When convenient for the anesthesia team, they will be surveyed about the ease of laryngoscopy. An independent observer will note the other 2 objective components of the survey.

8.3 Method for Assigning Subjects to Treatment Groups

REDCap will be used to randomize patients to one of two groups based on when providers will intubate (TOFC=1 and 2 minutes after rocuronium at 0.6 mg/kg).

8.4 Masking/Blinding of Study

This is an open-label pilot investigation. Masking and blinding procedures are not applicable.

8.5 Schedule of Events

	Schedule of Events	
Study Activity	Visit 1	Visit 2
Scheduled Intubation		X
Intubating conditions observation		X
Informed consent	X	
Review of Medical Record	X	
Adverse event evaluation		X

9 Statistical Plan

9.1 Sample Size Determination

Based on preliminary data, intubating score of 3 (ideal conditions) will occur in approximately 65% of patients in the two-minute group. With a sample size of 83 patients per group (166 patients total), we will have 80% power at the 5% significance level to detect a difference in this outcome of 20% (i.e. 65% vs. 85%) between the two-minute group and the other two treatment groups using a chi-square test. We will enroll 85 patients in each group (170 total) to account for possible dropouts.

9.1.1 Descriptive Statistics

Comparisons of intubating conditions will be made using a chi-square test.

9.1.2 Handling of Missing Data

This is a prospective pilot study and therefore we do not anticipate any missing data. In the event of any unexpected missing data, no attempt to impute this missing data will be made; missing data will simply be treated as missing in the statistical analysis, and replacement participants will be enrolled to achieve the target accrual of n=170 participants.

9.2 Subject Population(s) for Analysis

Each participant who goes through the surgery and completes monitoring of residual neuromuscular blockade will be included in the primary analysis regardless of study withdrawal for any reason. In the event of any study withdrawals, in secondary analysis we will examine the sensitivity of our results to the exclusion of patients who withdrew.

10 Safety and Adverse Events

10.1 Definitions

10.1.1 Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

10.1.2 Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

10.1.3 Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

10.1.4 Adverse Event Reporting Period

For this study, the follow-up period is defined as up to successful intubation.

10.1.5 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

10.1.6 Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

10.1.7 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the electronic case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

10.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures. Each participating site will report SAEs to their respective IRB or Ethics Committee with copy of submission and review provided to the leading site. Should there be any SAEs at any of the participating sites; the study team at that site will notify the primary site (Mayo Clinic in Florida) within 24 hours of learning of the event.

Any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO will be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

The following information will be collected on the adverse event worksheet (and entered in the research database):

- Study ID
- Disease
- The date the adverse event occurred
- Description of the adverse event
- Relationship of the adverse event to the research device*
- Determination if the adverse event was expected
- The severity of the adverse event (severity scale described below**)
- If any intervention was necessary
- Resolution (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

*** Relationship Index**

The relationship of an AE to the Investigational Device is a clinical decision by the sponsor-investigator (PI) based on all available information at the time of the completion of the eCRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the use and proper application of study device.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to use of the study device which makes a causal relationship improbable and in which use of other devices, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to use of the study device but which could also be explained by concurrent disease or use of other devices or chemicals.

4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to use of the study device, unlikely to be attributed to concurrent disease or use of other devices or chemicals.

5. Definite: a reaction that follows a reasonable temporal sequence from the use of the study device.

**** Severity Scale**

The maximum intensity of an AE during a day should be graded according to the definitions below and recorded in detail as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.

2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities but are usually ameliorated by simple therapeutic measures.

3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

10.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-

monitoring plan (see section 10 “Study Monitoring, Auditing, and Inspecting”). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

11 Data Handling and Record Keeping

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

11.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records and any forms completed specifically for this study.

11.3 Case Report Forms

All data necessary for this study will be obtained from EHR or at the time devices are being used and recorded on the electronic Case Report Forms (CRFs) created in REDCap. All missing data will be explained.

11.4 Data Management

Study data to be collected and managed using EHR and study-generated source documents and transcribed into electronic CRFs in REDCap, electronic data capture software, hosted by CTSA at Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Deidentified, raw data from TetraGraph’s internal memory card will also be collected and used for post-hoc analysis. This data will be stored within Mayo internal servers.

11.5 Data Processing

All study date will be stored and analyzed at Mayo Clinic in Florida using the REDCap electronic data capture tool.

11.6 Data Security and Confidentiality

All source documents including clinical findings, observations or other activities will be stored in a REDCap database that will be designed by an Investigator. Access to the REDCap database will be limited to the Principal Investigator, Investigators, Study Team members, and Statistician.

11.7 Data Quality Assurance

Once the study is completed the Principal Investigator will randomly select 3 participants and compare the data documented in the EHR with what is entered into the REDCap database. If there is any discrepancy, the Principal Investigator and/or Investigators will cross-reference all 170 patients to ensure accuracy.

11.8 Data Clarification Process

For any data query the Principal Investigator and Investigators will meet to clarify the data queried and make corrections based on consensus.

11.9 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. Principal Investigator will maintain regulatory and essential study documents to ensure compliance with local and federal policies/guidelines.

The sponsor-investigator will retain the specified records and reports:

- As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

12 Study Monitoring, Auditing, and Inspecting

12.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the compliance or quality assurance reviewer is given access to all the study-related documents.

12.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

13 Ethical Considerations

This study is to be conducted according to United States and International government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the individual obtaining the informed consent.

14 Study Finances

14.1 Funding Source

This investigator-initiated study is not funded. Study coordinator's time is supported by the Department of Anesthesiology and funding for statistical analysis will be provided from the Principal Investigator's research fund.

14.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

No financial conflicts of interested are anticipated or have been identified for this study.

14.3 Subject Stipends or Payments

No payment is given to study participants.

15 Publication Plan

The primary responsibility for publication of the study results is with the Primary Investigator. After the complication of study and prior to publication, the study results will be shared with all Investigators. The study will be registered at ClinicalTrials.gov prior to subject recruitment along with the posting of the results within 12 months of final data collection for the primary outcome measure.

16 References

1. Lieutaud T, Billard V, Khalaf H, Debaene B. Muscle relaxation and increasing doses of propofol improve intubating conditions. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2003;50(2):121-6.
2. Blobner M, Frick CG, Stäuble RB, Feussner H, Schaller SJ, Unterbuchner C, et al. Neuromuscular blockade improves surgical conditions (NISCO). Surgical Endoscopy. 2015;29(3):627-36.
3. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg. 2010;111(1):120-8.
4. Hayes AH, Mirakhur RK, Breslin DS, Reid JE, McCourt KC. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. Anaesthesia. 2001;56(4):312-8.
5. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology. 2003;98(5):1042-8.
6. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. Br J Anaesth. 2007;98(3):302-16.
7. Cammu G, De Witte J, De Veylder J, Byttebier G, Vandeput D, Foubert L, et al. Postoperative residual paralysis in outpatients versus inpatients. Anesth Analg. 2006;102(2):426-9.
8. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. Anesth Analg. 2008;107(1):130-7.
9. Berg H, Roed J, Viby-Mogensen J, Mortensen CR, Engbaek J, Skovgaard LT, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications

after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand. 1997;41(9):1095-103.
10. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear TD, Vender JS, et al. Residual Neuromuscular Block in the Elderly: Incidence and Clinical Implications. Anesthesiology. 2015;123(6):1322-36.
11. Todd MM, Hindman BJ, King BJ. The implementation of quantitative electromyographic neuromuscular monitoring in an academic anesthesia department. Anesth Analg. 2014;119(2):323-31.
12. Todd MM, Hindman BJ. The Implementation of Quantitative Electromyographic Neuromuscular Monitoring in an Academic Anesthesia Department: Follow-Up Observations. Anesth Analg. 2015;121(3):836-8.
13. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Marymont JH, Vender JS, et al. Intraoperative acceleromyography monitoring reduces symptoms of muscle weakness and improves quality of recovery in the early postoperative period. Anesthesiology. 2011;115(5):946-54.
14. 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):977-84.
15. Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology. 1997;87(5):1035-43.
16. Naguib M, Brull SJ, Kopman AF, Hunter JM, Fulesdi B, Arkes HR, et al. Consensus Statement on Perioperative Use of Neuromuscular Monitoring. Anesth Analg. 2018;127(1):71-80.
17. Nemes R, Nagy G, Murphy GS, Logvinov, II, Fulesdi B, Renew JR. Awake Volunteer Pain Scores During Neuromuscular Monitoring. Anesth Analg. 2019.
18. Grayling M, Sweeney BP. Recovery from neuromuscular blockade: a survey of practice. Anaesthesia. 2007;62(8):806-9.
19. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ. A survey of current management of neuromuscular block in the United States and Europe. Anesth Analg. 2010;111(1):110-9.
20. Brull SJ, Silverman DG. Real time versus slow-motion train-of-four monitoring: a theory to explain the inaccuracy of visual assessment. Anesth Analg. 1995;80(3):548-51.
21. Brull SJ, Silverman DG. Visual and tactile assessment of neuromuscular fade. Anesth Analg. 1993;77(2):352-5.
22. 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):1253-60.
23. Eriksson LI. Reduced hypoxic chemosensitivity in partially paralysed man. A new property of muscle relaxants? Acta anaesthesiologica Scandinavica. 1996;40(5):520-3.
24. Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: a prospective case study. Lancet (London, England). 2000;355(9205):707-11.

25. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J, et al. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand. 2007;51(7):789-808.

17 List of In-Text Tables

17.1 Intubating Conditions survey

Variable assessed	Evaluation of Intubating Conditions*		
Laryngoscopy**	Easy (1)	Fair (2)	Difficult (3)
Vocal cords position	Abducted (1)	Intermediate/moving (2)	Closed (3)
Reaction to insertion of the tracheal tube and cuff inflation (diaphragmatic movement/coughing)	None (1)	Slight[§] (2)	Vigorous/sustained[¥] (3)
Scoring:	Excellent	Good	Poor
	Clinically Acceptable		Not Clinically Acceptable

***Intubation conditions definitions**:
- Excellent: all qualities are excellent
- Good: all qualities are either excellent or good
- Poor: presence of a single quality listed under "poor"

****Laryngoscopy**
- Easy: jaw relaxed, no resistance to blade insertion
- Fair: jaw not fully relaxed, slight resistance to blade insertion
- Difficult: poor jaw relaxation, active resistance of the patient to laryngoscopy

[§]One of two weak contractions or movement for less than 5 s
[¥]More than two contractions and/or movement for longer than 5 s

17.2 Intraoperative Data

Study ID:	Date of Surgery (dd / mm / yyyy):		
Wrist circumference (right):	Wrist circumference (left):	Dominant side: L / R	
Age (yrs):	Weight (kg):	Height (cm):	IV side: L / R

	Time	**TetraGraph (TG)** **Arm L / R**
Calibrated baseline TOFR		
Supramax current after calibration (mA)		
Time to TOFC=3		
Time to TOFC=2		
Time to TOFC=1		
Time to TOFC=0		
Time to TOFC at 2 minutes		