Electromyographic and acceleromyographic monitoring in restricted arm movement surgical setting. A prospective, randomized trial.

NCT04352140

10MAY2021

Electromyographic and acceleromyographic monitoring in restricted arm movement surgical setting. A prospective, randomized trial.

Regulatory Sponsor Principal Investigator:	J. Ross Renew, MD
Funding Sponsor:	Departmental Resources
Protocol Number:	IRB # 20-000629
Study Product:	TetraGraph TOFScan

Initial version: [21Jan2020] Version **(1.0)**

Revision: [19Oct2020] Version (2.0)
Revision: [23Feb2021] Version (3.0)
Revision: [10May2021] Version (4.0)

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1 Protocol Approval Form

Protocol Number: 20-000629

Study Name: Electromyographic and acceleromyographic monitoring in restricted arm movement surgical setting. A prospective, randomized trial.

This protocol has been reviewed and approved by the following:

________________________ May, 2021

J. Ross Renew, MD Date

Principal Investigator

2 List of Abbreviations

AE	Adverse Event/Adverse Experience
AMG	Acceleromyography
CE	Conformite Europeene
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
KMG	Kinemyography
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
PTC	Post-tetanic count
SAE	Serious Adverse Event/Serious Adverse Experience
SGX	Sugammadex
SOP	Standard Operating Procedure
TOF	Train-of-four
TOFC	Train-of-four count
TOFR	Train-of-four ratio
UPIRTSO	Unanticipated Problems Involving Risk to Subjects or Others
VNRS	Verbal Numeric Rating Scale

3 Study Summary

Title	Electromyographic and acceleromyographic monitoring in restricted arm movement surgical setting. A prospective, randomized trial.
Running Title	Subjective vs. Objective
Phase	N/A
Methodology	Randomized, Open-Label
Overall Study Duration	12 months
Subject Participation Duration	2 – 5 hours
Single or Multi-Site	Multi site
Objectives	The primary aim of this study is to compare the ease of use and repeatability of AMG vs. EMG neuromuscular responses in surgical settings in which the patients' arm movement is restricted (placed under surgical drapes) in laparoscopic or robotic procedures.
Number of Subjects	105
Diagnosis and Main Inclusion Criteria	Patients undergoing elective robotic or laparoscopic surgery and requiring administration of neuromuscular blocking agents intraoperatively
Study Device	TetraGraph and TOFScan
Duration of Administration	Single stimulation of ulnar nerve repeated at specific intervals as outlined in the Study Procedures (Section 9.2)

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

Residual neuromuscular blockade is a common complication in the post-anesthesia care unit (PACU) when neuromuscular blocking agents (NMBAs) have been used in the operating room. The only method of reliably detecting residual neuromuscular blockade is through the use of quantitative neuromuscular monitors. 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.

The aim of this study is to determine the usability of two different monitors, the acceleromyography (AMG)-based TOFScan (which relies on muscle movement for measurement of function) and the electromyography (EMG)-based TetraGraph (which relies on measurement of electrical activity) in surgical settings in which access to the arms and hand muscle movements are restricted.

The TetraGraph (Senzime AB, Uppsala, Sweden) is a standalone EMG-based quantitative monitor that received Conformité Européene (CE) and FDA approvals. EMG measures electrical activity within the muscle following peripheral nerve stimulation and is unaffected by involuntary patient motion or restricted muscle movements from surgical positioning. The IntelliVue (Philips, Amsterdam, The Netherlands) is a modular AMG-based monitor that is being used routinely at Mayo Clinic for all surgical procedures in which NMBAs are administered. TOFScan (Draeger Medical Inc., Telford, PA) is another standalone AMG-based quantitative monitor available for routine clinical use in the United States. We plan to compare measurements obtained with Tetragraph and TOFScan monitors during surgical procedures in which the patients' arms are tucked under surgical drapes and access is limited. The comparison will be based on a validated usability scale, the System Usability Scale (SUS) Plus (Table 18.3 and Table 18.4) that was designed to rate the usability of medical devices.

The original System Usability Scale (SUS) was developed by John Brooke in 1986 (https://www.usabilitest.com/system-usability-scale), and it allows investigators to evaluate a wide variety of products and services, including hardware, software, mobile devices and websites. It is a simple, ten-item Likert scale with five response options for respondents; the responses vary from "Strongly agree" to "Strongly disagree." The scale provides a quick and reliable tool for measuring the usability of the product in question.

The usability of the two monitors will be determined throughout various stages of neuromuscular blockade, including onset of blockade following neuromuscular relaxant administration, maintenance, and reversal of blockade with sugammadex or neostigmine until adequate recovery (train-of-four ratio >0.9) is confirmed. At the end of each surgical case, the healthcare provider will be asked to rate the usability of the TetraGraph and the usability of the TOFScan monitors based on the ten items on the SUS scale.

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 demonstrated 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.

There are several types of quantitative neuromuscular monitors. These devices can be incorporated into the anesthesia workstation, allowing data to be seamlessly integrated into the electronic medical record. Unfortunately, this setup can preclude using these monitors in the PACU as portability is sacrificed. In contrast, other monitors exist as standalone, portable (hand-held) units.

Aside from portability, objective monitors can further be categorized based on the modality utilized to measure responses. Mechanomyography (MMG) measures the force of contraction of the adductor pollicis (thumb) muscle following ulnar nerve stimulation and has served as the traditional "gold-standard". Mechanomyographic responses are precise and reproducible, however the setup is cumbersome and the lack of commercially available devices has relegated MMG to strictly research purposes. Acceleromyography (AMG) measures acceleration of a muscle group (typically the thumb) in response to stimulation (typically the ulnar nerve). This technique is similar to MMG, but instead of measuring the force of muscle contraction, an accelerometer fixed to the thumb measures the acceleration of the thumb in response to ulnar nerve stimulation. Based on Newton's Second law that states force is proportional to acceleration, the measured acceleration is correlated with the force of contraction in the clinical setting. There are currently two standalone AMG-based monitors available for clinical use: the STIMPOD (Xavant Technologies, Pretoria, South Africa) and the ToFscan (Draeger Medical Inc., Telford, PA). These devices represent improvements in AMG technology over its predecessor, the TOF-Watch (Schering-Plough Corp., Kenilworth, NJ, USA) as they utilize three dimensional transducers that can better quantify the complex motion of the thumb. Despite these advances, the use of AMG can be limited due to patient positioning that precludes free motion of the thumb, as well instances of awakening patients moving their thumb during measurements. Kinemyography (KMG) is based on similar principles to AMG, and relies on the thumb being able to move freely. Upon neurostimulation, KMG utilizes a piezoelectric motion sensor that is bent between the thumb and index fingers following muscle contraction. The degree of this bending is quantified and used to determine a TOF ratio. While Datex-Ohmeda (Helsinki, Finland) manufactures a KMG device that can be incorporated into the anesthesia work station, there are no currently available standalone KMG devices. Electromyography (EMG) devices measure electrical activity, termed compound muscle action potentials (cMAPs) following nerve stimulation (typically at the adductor pollicis muscle after ulnar nerve stimulation). 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. We have previously investigated this device and presented our findings at several annual meetings such as International Anesthesia Research Society (May 2018, May 2017, May 2013), the Society for Technology in Anesthesia (January 2018), and the American Society of Anesthesiologists (October 2017, October 2012), European Society of Anaesthesiology (June 2018, June 2015) (17). Furthermore, we have recently submitted abstracts to the PostGraduate Assembly in Anesthesiology in December 2018 as well as a manuscript describing a multi-center, volunteer study investigating TetraGraph versus AMG-based monitors. Our work thus far has found this device to be easy to apply, reliable, and able to provide comparable measurements to other quantitative monitors.

Many clinicians default to the antiquated 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 acceleromyographic and electromyographic responses to train-of-four stimulation of the ulnar nerve in surgical settings where the arm movement is restricted by the surgical drapes (such as laparoscopic and robotic surgery). The time points of interest will include the onset of blockade following neuromuscular relaxant administration, maintenance of block, and reversal of blockade with sugammadex or neostigmine until adequate recovery (train-of-four ratio >0.9). The reliability of the two monitors will be evaluated post hoc by comparing the repeatability of responses, and the usability of the two monitors will be evaluated by the healthcare providers using the System Usability Scale (SUS) Plus scale, a simple, 10-item Likert scale with 5 response options for the evaluators (https://www.usabilitest.com/system-usability-scale).

4.3 Risks and Benefits

- The benefits of using neuromuscular blockade monitoring devices:
  Early detection of optimal time for tracheal extubation; optimal management of intraoperative depth of neuromuscular block to facilitate surgical procedures; determination of appropriate time and dose of sugammadex reversal; and detection of residual neuromuscular blockade. This is currently the standard of care practice at Mayo Clinic.
- The risks of using neuromuscular blockade monitoring devices:
  Slight discomfort when electrical stimulation is administered in awake volunteers; however, our patients will be anesthetized, rendering this risk as extremely minor.

5 Study Objectives

Primary Objective
Compare the objective EMG-derived data using TetraGraph (TOFR, TOFC, PTC) with those obtained from the AMG-based TOFScan monitor and assess the reliability and usability of the two objective monitors.

Secondary Objective
Determine the incidence of failure to calibrate and monitor neuromuscular responses using the two monitors.

6 Study Design

6.1 General Description

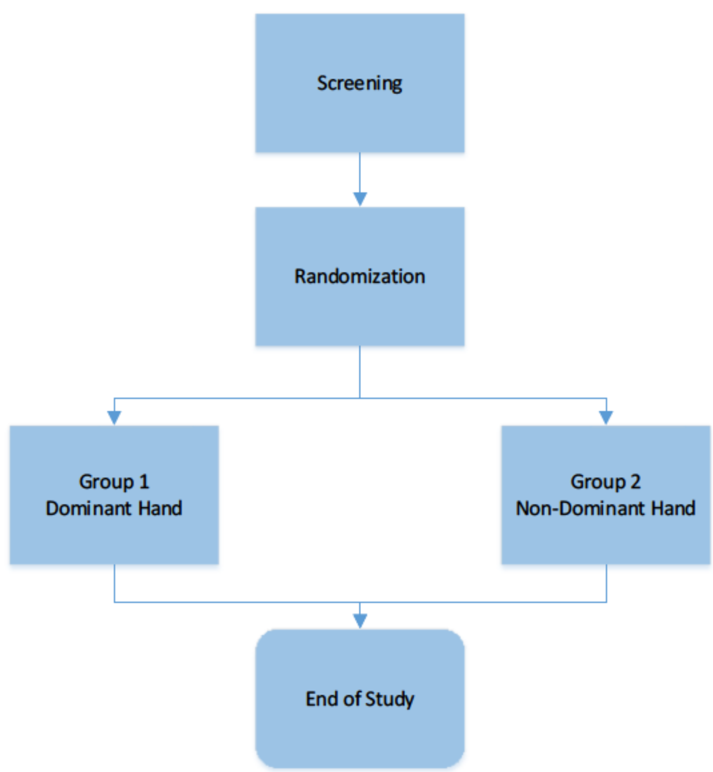
This unblinded, multi center, prospective, randomized, observational study will involve 35 patients undergoing surgical procedure that involved administration of neuromuscular blockade agents intraoperatively in surgical settings in which the patients' arms are placed under surgical drapes and are unavailable to the anesthesiologist. These surgical procedures include laparoscopic and robotic surgeries.

6.2 Number of Subjects

One hundred five (105)

6.3 Duration of Participation

2-5 hours, depending on duration of surgery



6.4 Primary Study Endpoints

The primary endpoint of the study will be to determine the usability of the two monitors using the SUS Plus scale.

6.5 Secondary Study Endpoints

The secondary endpoint is to determine the reliability of the two monitors, by comparing the frequency of each monitor's failure to calibrate and measure evoked responses.

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 18.2). These will include type and total dose of NMBA used, time and dose of last NMBA administration, time and dose of specific reversal agent administration, time of tracheal extubation, and TOF ratio at the time of extubation (if available).

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 an elective laparoscopic or robotic surgical procedure that requires use of NMBA agents 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 or leg into the sterile field

7.3 Subject Recruitment, Enrollment and Screening

On a daily basis, there are over 20 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 3 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 Device

8.1 Description

TetraGraph (Figure 19.1) device is a FDA approved neuromuscular transmission monitor capable of measuring the depth of neuromuscular block in anesthetized patients who received neuromuscular blocking agents. TetraGraph uses EMG to measure the muscle action potentials that are generated in response to electrical neurostimulation via skin (ECG) electrodes. TetraGraph data is recorded on the monitor's built-in SD card, and all intraoperative data will be recorded and later downloaded for purposes of analysis. The recorded data do not contain PHI, only the date/time of recording, and any additional intraoperative interventions, such as the time of NMBA dose administration, time of antidote administration, time of extubation, etc. These events are flagged in the monitor's integrated SD card recordings.

TetraGraph uses EMG to measure the muscle action potentials that are generated in response to percutaneous electrical neurostimulation, and is not subject to the limitations imposed by the AMG-based monitors: the measurement of the electrical compound muscle action potentials (cMAPs) can be made even when the thumb movement is restricted.

The TOFScan (Figure 19.2) is a neuromuscular transmission monitor that is based on AMG technology, and is used routinely in clinical care at Mayo Clinic. It can measure and record the evoked responses (acceleration) of the hand muscle adductor pollicis (thumb) and calculate the degree of neuromuscular block (the TOF ratio).

8.2 Method for Assigning Subjects to Treatment Groups

This is an open-label investigation and all study participants are assigned to both TetraGraph and TOFScan devices. The randomization involves the use of dominant vs non-dominant arm for the placement of TetraGraph device.

The randomization will be performed utilizing REDCap and assigned anesthesia clinical care team will be informed of patients' assigned to guide them with the selection of the assigned treatment option.

8.3 Masking/Blinding of Study

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

9 Study Procedures

9.1 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.

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

- Elective surgical procedure as in which intraoperative access to the arms is restricted because of surgical draping.
- Anesthetic management will be standardized to utilize rocuronium, sevoflurane, and sugammadex or neostigmine at the discretion of the attending anesthesiologist
- Prior to induction of anesthesia, the Tetragraph electrodes will be placed over the ulnar nerve and the thumb to measure the response of adductor pollis nerve. Randomization will be performed utilizing REDCap and involves the use of dominant vs non-dominant arm.

- Following induction of anesthesia but prior to NMBA administration, baseline values will be recorded from both monitors after calibration.
- Anesthesia providers will have access to the TetraGraph and TOFScan values during the entire procedure, and will make clinical decisions as per usual clinical routine at Mayo Clinic.
- After NMBA administration, sets of measurements will be taken with the two monitors at regular intervals (every 12 sec, 20 sec, 1 min, 15 min, etc.) as required per usual clinical routine and determined by the anesthesia attending.
- Near the conclusion of the operation but prior to the reversal of neuromuscular block, another set of measurements will be taken, with the two monitors, as per usual clinical routine, in order to determine the appropriate reversal drug dosage.
- After sugammadex or neostigmine administration, measurements will be taken every 20 seconds until return of neuromuscular function is documented.
- Following documentation of adequate neuromuscular function (TOF ratio is >0.9,) the devices will be removed and the patient will proceed along the standard recovery pathway.

9.3 Schedule of Events

	Schedule of Events	
Study Activity	Visit 1	Visit 2
Tetragraph		X
TOFScan		X
Informed consent	X	
Review of Medical Record	X	
Adverse event evaluation		X

10 Statistical Plan

10.1 Sample Size Determination

Based on paired t-test, 23 enrolled patients will give 90% power to detect a difference in TOF ratios with a significance level of 0.05 (JMP Pro Software version 13.0.0 [August 23, 2018]; SAS Institute Inc., Cary, NC). We utilized a standard deviation of 0.07 that was determined during our multi-center volunteer study comparing another AMG device and TetraGraph. However, each participating center will enroll 35 patients to take into account patient loss or missing data. The total number of patients for this study from all 3 centers will be aimed at 105 participants.

10.2 Statistical Methods

10.2.1 Descriptive Statistics

Analysis of agreement between the two monitors will be assessed using Bland-Altman. The limits of agreement are defined as bias ± 2 SD, where SD denotes the standard deviations of the differences. Limits of agreement are interpreted as the reference range within which 95% of the differences will lie. The bias and the limits of agreements surrounding the bias (± 2 SD) will be calculated with 95% confidence intervals. Statistical significance will be defined as a p-value <0.05. Comparison of the usability of the two monitors will be made using the System Usability Scale (SUS) Plus. The SUS is particularly relevant to user experience when comparing two monitors that are based on different technologies (AMG and EMG). It will allow us to make a comparison of the two monitors in a surgical setting in which access to the monitoring muscle site (the thumb and hand) is limited. Because SUS is technology-neutral, we will be able to continue to use it in usability testing as technology evolves over the years, allowing us to continually evaluate and select the optimal monitoring technology available.

10.2.2 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=35 participants.

10.3 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.

11 Safety and Adverse Events

11.1 Definitions

11.1.1 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.

11.1.2 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.

11.1.3 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**.

11.1.4 Adverse Event Reporting Period

For this study, the follow-up period is defined as up to 10 minutes after arrival to PACU or TOF ratio is > 0.9 (whichever occurs first).

11.1.5 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.

11.1.6 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.

11.1.7 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.

11.2 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 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.

11.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated 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.

11.3.1 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 details 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.

11.4 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.

12 Data Handling and Record Keeping

12.1 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.

12.2 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.

12.3 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.

12.4 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.

12.5 Data Processing

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

12.6 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.

12.7 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 35 patients to ensure accuracy.

12.8 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.

12.9 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]

13 Study Monitoring, Auditing, and Inspecting

13.1 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.

13.2 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.

14 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.

15 Study Finances

15.1 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.

15.2 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.

15.3 Subject Stipends or Payments

No payment is given to study participants.

16 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.

17 References

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18 List of In-Text Tables

18.1 Schedule of Events

	Schedule of Events	
Study Activity	Visit 1	Visit 2
Tetragraph		X
TOFScan		X
Informed consent	X	
Review of Medical Record	X	
Adverse event evaluation		X

18.2 Intraoperative Data

Study ID:	Date of Surgery (dd / mm / yyyy):	Examiner's Initials:	
Wrist circumference (right):	Wrist circumference (left):	Dominant side: L / R	
Ankle circumference (right):	Ankle circumference (left):		
Age (yrs):	Weight (kg):	Height (cm):	BMI:
Muscle relaxant name:			
Muscle relaxant total dose (mg):			
Time of first muscle relaxant dose (mm : hh):	: am / pm		

Reversal agent name:	
Reversal agent dose (mg):	
Time of reversal agent administration (mm : hh):	: am / pm
Time of extubation:	: am / pm

TetraGraph (TG) / TOFScan

	Time	**TetraGraph (TG)** **Arm L / R**	**TOFScan** **Arm L / R**	**TOFR # 3 (if needed)**
Calibrated baseline TOFR and supramax current				
TOFC=0 (post initial dose of NMBA)				
Time Interval (first recheck)				
Time Interval (second recheck)				
Time Interval				
Time Interval				
Time Interval				

Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				
Time Interval				

Time Interval				
pre-SGX				
+60sec after SGX				
+120 sec after SGX				
+180 sec after SGX				
+260 sec after SGX				
Extubation				
Time to recovery following SGX (TOFR ≥0.9)				
T0 (on arrival to PACU)				
T5 (5 min after PACU arrival)				
T10 (10 min after PACU arrival)				

18.3 Tetragraph SUS

Question	Rating						
		1	2	3	4	5	
I think that I would like to use TetraGraph frequently.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I found TetraGraph unnecessarily complex.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I thought TetraGraph was easy to use.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I think that I would need the support of a technical person to be able to use TetraGraph.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I found the various functions in TetraGraph were well integrated.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I thought there was too much inconsistency in TetraGraph.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I would imagine that most people would learn to use TetraGraph very quickly.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I found TetraGraph very cumbersome to use.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I felt very confident using TetraGraph.	Strongly Disagree	○	○	○	○	○	Strongly Agree
		1	2	3	4	5	
I needed to learn a lot of things before I could get going with TetraGraph.	Strongly Disagree	○	○	○	○	○	Strongly Agree

18.4 TOFScan SUS

Question	Rating						
I think that I would like to use TOFScan frequently.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I found TOFScan unnecessarily complex.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I thought TOFScan was easy to use.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I think that I would need the support of a technical person to be able to use TOFScan.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I found the various functions in TOFScan were well integrated.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I thought there was too much inconsistency in TOFScan.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I would imagine that most people would learn to use TOFScan very quickly.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I found TOFScan very cumbersome to use.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I felt very confident using TOFScan.		1	2	3	4	5	
	Strongly Disagree	○	○	○	○	○	Strongly Agree
I needed to learn a lot of things before I could get going with TOFScan.		1	2	3	4	5	

	Strongly Disagree ○ ○ ○ ○ ○ Strongly Agree

19 List of In-Text Figures

19.1 TetraGraph

19.2 TOFScan