Comparison of the ToFscan and TetraGraph during Recovery of Neuromuscular Function in the Post Anesthesia Care Unit

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1 Protocol Approval Form

Protocol Number: 18-011298

Study Name: Comparison of the ToFscan and TetraGraph during Recovery of Neuromuscular Function in the Post Anesthesia Care Unit

This protocol has been reviewed and approved by the following:

J. Ross Renew, MD
Principal Investigator

10.23.19
Date

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
EMG	Electromyography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HER	Electronic Health Record
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
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
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
TOF	Train-of-four
UPIRTSO	Unanticipated Problems Involving Risk to Subjects or Others
VNRS	Verbal Numeric Rating Scale

3 Study Summary

Title	Comparison of the ToFscan and TetraGraph during Recovery of Neuromuscular Function in the Post Anesthesia Care Unit
Running Title	ToFscan vs TetraGraph
Phase	N/A
Methodology	Randomized, Open-Label
Overall Study Duration	6 months
Subject Participation Duration	Less than 1 hour
Single or Multi-Site	Multicenter International
Objectives	The primary aim of this study is to assess the agreement and repeatability between TOF values obtained from ToFscan and TetraGraph
Number of Subjects	120 (40 per site)
Diagnosis and Main Inclusion Criteria	Patients undergoing an elective surgery and requiring administration of NMBA intraoperatively
Study Device	TetraGraph
Duration of Administration	Single stimulation of ulnar nerve repeated at specific intervals as outlined in the Study Procedures (Section 6.2)
Reference therapy	ToFscan
Statistical Methodology	This pilot study is meant to be descriptive and it aims to collect basic data for future larger study

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 occurrence 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. For instance, there is a paucity of quantitative neuromuscular monitors commercially available. Also, two modalities of quantitative monitoring, kinemyography and acceleromyography, rely on movement of the muscles of interest, a characteristic frequently compromised during patient positioning for surgical procedures or in uncooperative awake patients in the PACU. Additionally, many clinicians are unfamiliar with these quantitative monitors, and incorporating them into their practice can represent an undesirable educational burden. The aim of this investigation is to compare the performance of two quantitative monitors utilized on post-anesthesia recovering patients. The ToFscan (Draeger Medical Inc., Telford, PA) represents one of the few standalone acceleromyography (AMG)-based quantitative monitors available for routine clinical use in the United States. The TetraGraph (Senzime AB, Uppsala, Sweden) is a standalone electromyography (EMG)-based quantitative monitor that recently received Conformité Européene (CE) approval. While both of these quantitative monitors can be utilized to guide intraoperative NMBA re-dosing and confirm recovery, they provide their objective data via drastically different techniques. AMG, based on Newton's Second law which describes force being proportional to acceleration, measures acceleration of the thumb and requires its unobstructed movement. As such, performing AMG in awake, uncooperative patients can yield inaccurate results because of unwanted patient movement. Alternatively, EMG measures electrical activity within the muscle following peripheral nerve stimulation, and is unaffected by involuntary patient motion. We plan to compare measurements with these two devices throughout various stages of neuromuscular recovery in the PACU end compare the usefulness of these devices in this vulnerable patient population.

4.2 Background

Postoperative residual weakness from neuromuscular blockade continues to be a common problem in the post-anesthesia care unit (PACU). Despite the routine use of reversal agents, a significant number of patients continue to arrive in the PACU with objective evidence of residual neuromuscular blockade (Naguib, Kopman, and Ensor 2007; Cammu et al. 2006). While not every patient with residual weakness develops a postoperative complication, many can develop

avoidable critical respiratory events (Murphy et al. 2008; Berg et al. 1997). Furthermore, special populations such as the elderly, are at particular risk for developing complications related to postoperative residual weakness (Murphy et al. 2015). The use of quantitative monitoring has been demonstrated to reliably reduce the incidence of postoperative residual weakness and the ensuing complications (Todd, Hindman, and King 2014; Todd and Hindman 2015; Murphy et al. 2011). 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 (Naguib et al. 2018).

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 (Sundman et al. 2000; Eriksson et al. 1997). Although evidence strongly suggests objective monitors should be used perioperatively whenever NMBAs are administered, these devices can be expensive and require additional training. Many clinicians default to the antiquated practice of utilizing qualitative (subjective) neuromuscular stimulating units such as a peripheral nerve stimulator (PNS) (Grayling and Sweeney 2007; Naguib et al. 2010).

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 recently received *Conformité Européene* (CE) approval. 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 (Octotober 2017, October 2012), European Society of Anaesthesiology (June 2018, June 2015). 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.

Utilizing recommendations from the Good Clinical Practice (GCP) Guidelines for monitoring of neuromuscular function (Fuchs-Buder et al. 2007), we will investigate the performance of the TetraGraph in patients recovering from anesthesia in the PACU. The postoperative setting is particularly important, as several previous studies performed in awakening patients have reported discordant TOF ratios: accelerographic TOF ratios were not an accurate representation of the neuromuscular status (recovery) of the patients (Baillard et al. 2004). We plan to compare two portable quantitative monitors, the EMG-based TetraGraph and the AMG-based ToFscan. ToFscan has recently been described as an acceptable surrogate for research purposes to the frequently used TOF-Watch (Murphy et al. 2018). The TOF-Watch monitor, however, is no longer manufactured, while the ToFscan is commercially available and approved by the United States Food and Drug Administration (FDA). While the ToFscan has a three-dimensional sensor that can measure acceleration in multiple planes, it still has the same limitations associated with muscle movement inherent to AMG-based quantitative monitors. This is of particular importance in the recovery room when patients may not be fully cooperative when quantitative monitoring is warranted to exclude postoperative residual weakness as a cause of patient distress.

4.3 Risks and Benefits

- The benefits of using neuromuscular blockade monitoring devices:
  Early detection of residual neuromuscular blockade
- The risks of using neuromuscular blockade monitoring devices:
  Slight discomfort when electrical stimulation is administered

5 Study Objectives

Primary Objective
To assess the agreement and repeatability between TOF values obtained from the ToFscan and TetraGraph during recovery from neuromuscular blockade as measured upon arrival to the PACU, and then 5 (+5 min) and 10 (+10 min)) minutes later.

Secondary Objective
Determine the incidence of postoperative residual weakness in the PACU (defined as TOFR <0.90).
Assess patient discomfort associated with each neurostimulation utilizing a verbal numeric rating scale (VNRS) from 0-10.

6 Study Design

6.1 General Description

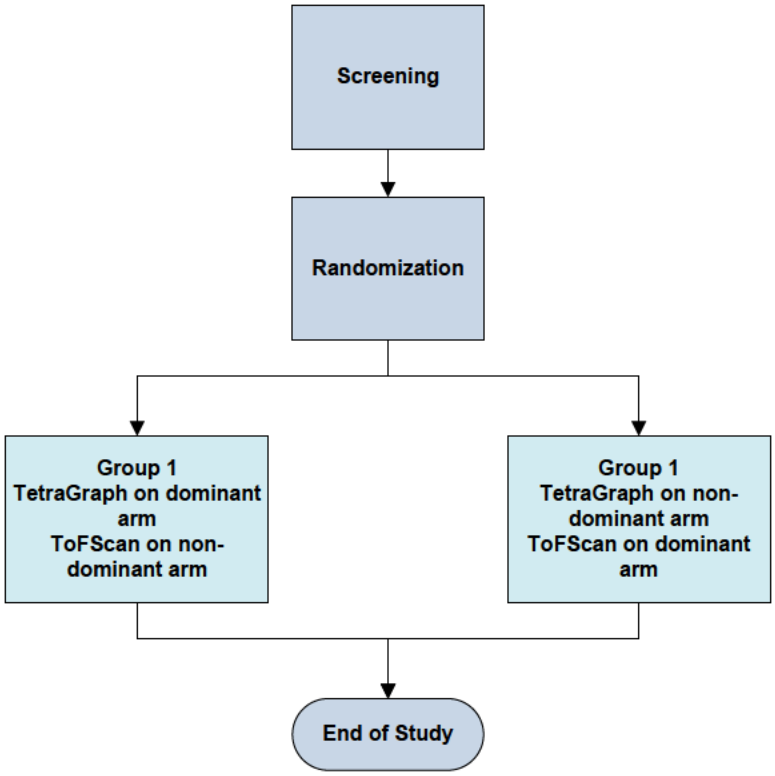
This unblinded, multicenter international, prospective, randomized, observational study will involve 120 patients undergoing surgical procedure that involved administration of neuromuscular blockade agents intraoperatively.

6.2 Number of Subjects

One hundred twenty (forty per site).

6.3 Duration of Participation

10 minutes in PACU



6.4 Primary Study Endpoints

The primary endpoint of the study will be the repeatability of values obtained by ToFscan and TetraGraph monitors.

6.5 Secondary Study Endpoints

The secondary endpoints of the study are the patient outcomes in the postoperative period and discomfort associated with the use of the devices.

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 in the PACU based on the ToFscan and TetraGraph devices (Table 15.3), several intraoperative characteristics will also be extracted from the medical record (Table 15.2). 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 surgical procedure that requires use of non-depolarizing NMBA agents administered intraoperatively.

7.2 Exclusion Criteria

- Patients with unilateral 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.

7.3 Subject Recruitment, Enrollment and Screening

Subjects will be enrolled from the Departments of Anesthesiology at the Mayo Clinic in Florida, NorthShore University Health System, and University of Debrecen. The study has an accrual target of 120 patients. On a daily basis, there are over 20 elective surgical cases performed at Mayo Clinic in Florida and thus no difficulties in accrual based on historical volumes are anticipated. Each participating center reviewed the feasibility and determined that approximately 3 participants per week will be completed for this study. The initial accrual period will last at least 3 months. 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 PACU, 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

ToFscan is a nerve stimulator module used for the measurement of neuromuscular transmission via accelerometry. ToFscan was developed by Drager Technologies, Canada, and it uses a three-dimensional piezoelectric sensor that attaches to the thumb via a hand adapter to measure acceleration in multiple planes (Murphy et al, 2018).

TetraGraph device is a neuromuscular transmission monitor capable of estimating 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 percutaneous electrical neurostimulation.

8.2 Method for Assigning Subjects to Treatment Groups

This is an open-label pilot investigation and all study participants are assigned to both standard of care and investigational device use in PACU. The randomization involves the use of dominant vs non-dominant arm.

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 per standard of care
- Intraoperative neuromuscular blockade, management, and neuromuscular antagonism will be at the discretion of the attending anesthesiologist.
- Upon arrival to the PACU, consenting patients will be randomized to have the TetraGraph placed on either their dominant or non-dominant arm TetraGraph uses proprietary, single-use surface electrodes (TetraSens^{TM}, Senzime AB, Uppsala, Sweden) with stimulating electrodes placed over the ulnar nerve, a reference electrode placed on the adductor pollicis (1st digit) (Figure 16.1). The skin will be prepped with careful abrasion and cleansing of the skin in the usual fashion prior to electrode placement.
- ToFscan will be placed on the patient's opposite arm. Stimulating electrodes (Red Dot ECG electrodes, 3M, St. Paul, MN) will be placed over the ulnar nerve with the negative electrode near the wrist crease and positive electrode placed 3-4 cm proximally. The skin will be prepped with careful abrasion and cleansing of the skin in the usual fashion prior to electrode placement. The ToFscan utilizes a thumb splint with the encased transducer secured to the hand (Figure 16.2).
- To obtain measurements with TetraGraph, TOF stimulation will be performed at 50mA and the measurement recorded. This measurement will be repeated twice, 20 seconds apart. If the two measurements differ by >10%, a third measurement will be recorded, with the closest two readings kept and the outlier discarded. If TetraGraph yields a train-of-four count but not a ratio with any measurement, this will be recorded.
- To obtain ToFscan measurements, TOF stimulation will be performed and the measurement recorded. According to the manufacturer, the ToFscan does not require calibration, and the default stimulating current is 50 mA. The TOF measurement will be repeated twice, 20 seconds apart. If the measurements differ by >10%, a third measurement will be repeated, with the closest two readings kept and the outlier discarded. If TetraGraph yields a train-of-four count but not a ratio with any measurement, this will be recorded.
- Each neurostimulation with the TetraGraph and ToFscan will be conducted simultaneously with two observers. Patients will be queried as to the level of discomfort associated with obtaining measurements (Figure 16.3). We have previously utilized this scoring system for a large, multi-center volunteer trial (manuscript submitted). If patients are unable to quantify their discomfort, this will be documented.
- The above described process will be repeated for both monitors upon arrival to PACU and after 5 minutes and 10 minutes into the PACU stay.

- ToFscan is an FDA approved monitor, while TetraGraph is CE marked, but not FDA approved yet. If TOF ratios below 0.9 are obtained with the ToFscan at any point during this study, the attending anesthesiologist will be notified, as per usual clinical routine. Possible actions include continued monitoring and supportive care, additional reversal agent administration, or, in extreme cases of weakness, ventilatory support with bilevel positive airway pressure (BiPAP) or tracheal re-intubation.
- Following measurements obtained with both devices at these specified time intervals and assuming TOF ratio is >0.9, the devices will be removed and the patient will proceed along the standard recovery pathway.
- If at any point the patient describes the discomfort associated with neurostimulation as a verbal numeric score of 7 or higher, the patient will be given the option to discontinue the study.
- Prior to discharge from PACU, patients will be asked to recall if they had a neurostimulation. If they do recall it, we will again query the level of discomfort associated with obtaining measurements (Figure 16.3).

9.3 Schedule of Events

	Schedule of Events	
Study Activity	Visit 1	Visit 2
ToFscan and Tetragraph		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, we will enroll 40 patients at 3 sites for a total of 120 patients to account for dropout during the study and to provide further insight into the incidence of postoperative residual weakness and three large centers. The other centers that might be submitting similar studies and

sharing de-identified data for the purposes of data analysis and publication are as follows: NorthShore University HealthSystem, Evanston, IL, USA [redacted] and University of Debrecen, Debrecen, Hungary [redacted]. Each site will complete separate applications for their IRB or Ethics committee approval; Mayo Clinic in Florida will serve as the lead site and will provide oversight to ensure compliance with the protocol at each site. .

10.2 Statistical Methods

Descriptive Statistics

Analysis of agreement between the devices will be assessed using the method described by Bland and Altman (Olofsen et al. 2015). The bias is defined as the mean difference of repeated measurements from the ToFscan and the TetraGraph obtained at the same time intervals. 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. Repeatability between the two devices at the various time intervals will also be assessed with significance defined as a p-value <0.05.

Handling of Missing Data

This is a prospective 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.

10.3 Subject Population(s) for Analysis

Each participant who goes through the recovery processes in the PACU 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 10 minutes following the arrival in the PACU.

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 (at each participating site) 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.

Each center will enter data into Mayo Clinic developed REDCap database. The administrator for REDCap added external users with their unique username and Data Access Groups (DAGs) were

created to ensure centers were only able to access their own data. Mayo Clinic Florida will have access to the entire de-identified data set.

Each center is designated a site number and the following naming convention for the records will be used:
01-XXX – First two digits for site number and last three digits sequential subject files (starting at 001). Mayo Clinic Florida will use the following format for their subject files: 01-001, 01-002, etc.
See Table with the list of participating centers and site number to identify correct naming conventions for the subject files.

12.5 Data Processing

All study date will be stored and analyzed at Mayo Clinic in Florida using the REDCap electronic data capture tool. De-identified data will be shared with investigators conducting similar study at their institution for the purposes of combined data analysis and publication.

Study center at NorthShore will not be entering any PHI in REDCap, specifically the date of birth and date of surgery will not be entered by this center into REDCap. A free-text to enter age will be the designated field for the NorthShore center to enter.

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 30 patients to ensure accuracy.

Participating centers will be asked to provide de-identified/redacted source documents for selected subjects for verification of data.

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. Each site's 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:

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

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.

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.

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18 List of In-Text Tables

18.1 Schedule of Events

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

18.2 Intraoperative Data

Study ID:			
Examiner Initials:		Date (dd / mm / yyyy):	
Muscle relaxant name:			
Muscle relaxant total dose (mg):			

Time of last 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
TOF ratio / TOF count at the time of reversal (if available):	
Monitor used during reversal:	PNS / IntelliVue NMT / ToFscan / None
Site of monitoring during reversal:	Hand / Face / Leg
TOF ratio / TOF count at the time of extubation (if available):	
Monitor used at extubation:	PNS / IntelliVue NMT / ToFscan / None
Site of monitoring:	Hand / Face / Leg

18.3 PACU data

Study ID	
Date of Surgery (dd / mm / yyyy):	

Initials:		Dominant side:	L / R	Age (yrs):	
Weight (kg):		Height (cm):		BMI:	

TetraGraph (TG) Arm tested: dominant / non-dominant

	TOFR #1	TOFR #2	TOFR #3 (if needed)	VNRS
T0 (on arrival to PACU)				
T5 (5 min later)				
T10 (10 min later)				
Predischarge VNRS	xxx	xxx	xxx	

ToFscan (TS) Arm tested: dominant / non-dominant

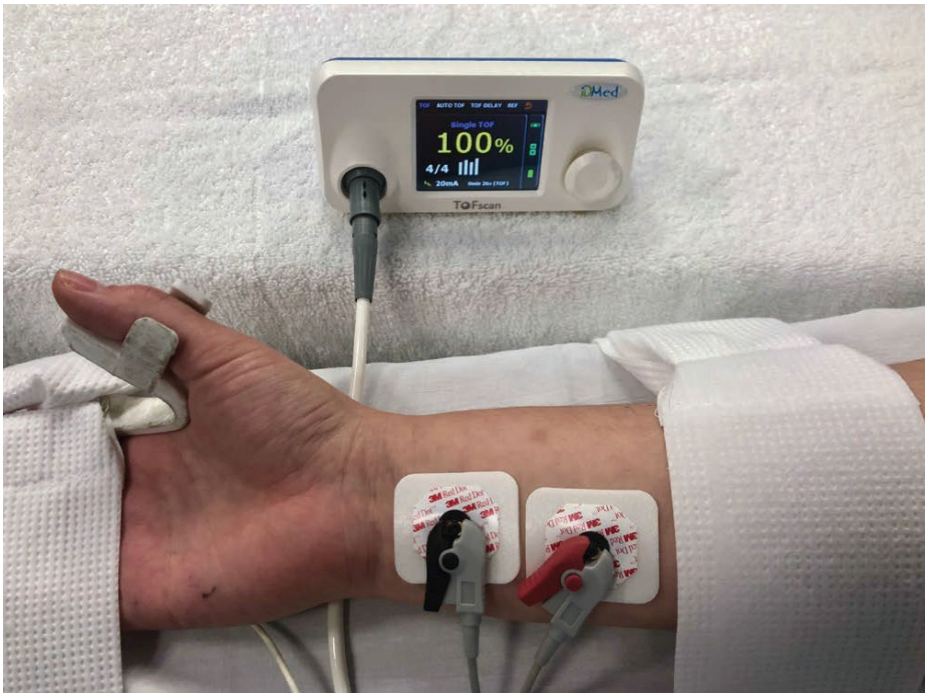
	TOFR #1	TOFR #2	TOFR #3 (if needed)	VNRS
T0 (on arrival to PACU)				
T5 (5 min later)				
T10 (10 min later)				
Predischarge VNRS	xxx	xxx	xxx	

TG= TetraGraph; TS= ToFscan; TOFR= train-of-four ratio; VNRS= verbal numeric rating scale

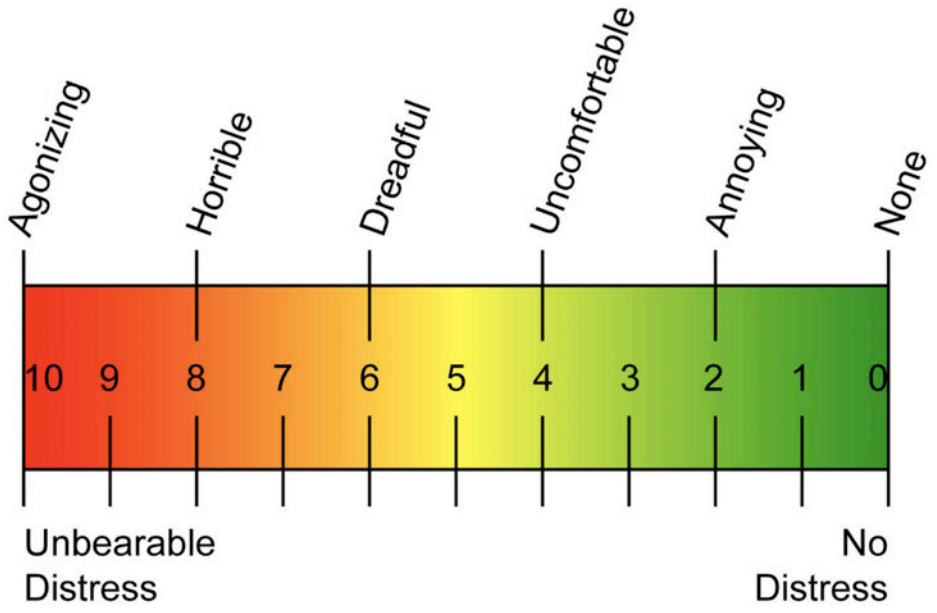
19 List of In-Text Figures

19.1 TetraGraph

19.2 ToFscan



19.3 VNRS


Agonizing
Horrible
Dreadful
Uncomfortable
Annoying
None
10 9 8 7 6 5 4 3 2 1 0
Unbearable Distress
No Distress