MSK PROTOCOL COVER SHEET

A Randomized Controlled Trial to Compare the Effectiveness of Deep vs Moderate Neuromuscular Blockade in Reducing Postoperative Pain and Intra-abdominal Insufflation Pressure during Minimally Invasive Robotic Prostatectomy

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

The objective of this randomized controlled trial is to compare the effectiveness of deep ves moderate neuromuscular blockade (NMB) in reducing postoperative pain and intra-abdominal insufflation pressure in patients undergoing minimally invasive robotic prostatectomy.

Patients will be randomized into two groups: deep (intervention) versus moderate (control) NMB. In both groups, anesthesia will be induced and maintained per our department's routine and standarized as per outlined in the study design. We plan to randomize 130 patients to ensure 120 evaluable patients for each of the two primary endpoints. Enrollment of patients will be limited to Josie Robertson Surgery Center.

For each patient in either arm of the study, rocuronium infusion will not be started until there is sign of spontaneous recovery from induction dose of muscle relaxant. "Sign of spontaneous recovery" will include any twitch on Train of four (TOF) OR post tetanic stimulation. Depth of blockade will be monitored continuously with a Train-of-Four (TOF) General Electric (GE) Neuromuscular transmission (NMT) Anandic device. Rocuronium will be continuously infused and titrated according to group assignment: (i) The intervention group will have rocuronium titrated to deep paralysis defined as post tetanic count of 1-2. (ii) The control group will have rocuronium infusion titrated to moderate paralysis defined as TOF of 1-2.
All patients will be maintained in the same surgical position (angle of Trendelenburg) per robotic urological surgery standard. An initial starting intra-abdominal pressure (IAP) value will be set. All cases will begin at this value, which will be less than 10 but above 8 mm Hg. To prevent surgeon bias in initial IAP, the surgeon will be blinded to the starting IAP value. As necessary, surgeons will request an increase in pressure to improve visualization. The IAP values will be recorded at 15-minute intervals. Changes in IAP outside the 15-minute interval measurement point will also be recorded. Any request by surgeon to change IAP will be recorded independent of an actual change. The IAP value will be concealed with black tape to maintain surgeon blinding throughout the duration of the case. Increases or decreases in IAP per surgeon's request will be allowed throughout the case with scripted responses. Surgical exposure/visualization will be assessed at 30-minute intervals using the Leiden surgical rating scale of 1 to 5.

At the end of a case, patients in both arms will be reversed with sugammadex at fascia closure (i.e. all port sites are closed). Estimated blood loss will be extracted from Electronic Medical Record. Postoperatively, endpoints will be recorded on all patients by the PACU nurse and research staff according to established pain and nausea scales.. Estimated time to completion of accrual is 1 year.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

This study will be conducted on patients undergoing minimally invasive robotic prostatectomy:

Two Primary Objectives:

1) Investigate if different levels of IAP will be utilized when performing robotic prostatectomy in patients under a moderate NMB technique vs. patients under a deep NMB technique.
2) Investigate if there is a difference in patient-reported postoperative pain in patients under moderate NMB vs. patients under deep NMB during robotic prostactectomy.

Secondary Objectives:

1) Investigate if there is a difference in surgeon assessment of surgical exposure when performing surgery under deep vs. moderate NMB
2) Investigate and compare various exploratory endpoints between deep and moderate NMB. These endpoints include: the total dose of analgesics during the procedure, the total dose of analgesics

postoperatively, postoperative shoulder pain, total intraoperative blood loss, operating time, postoperative nausea, time to the first *postoperative* antimetic, total dose of antiemetics postoperatively, and postoperative RASS scores (Richmond Agitation Sedation Scale)

Primary Hypotheses:

1) Patients who undergo surgery with a deep NMB technique will report lower postoperative pain.
2) Surgeons will operate at lower levels of intra-abdominal pressure under deep NMB technique.

Secondary Hypotheses:

1) Deep NMB will result in improved surgical exposure (assessed by the surgeon) during robotic surgery
2) There will be an improvement in outcomes of various exploratory endpoints as a result of deep NMB. These endpoints include: the total dose of analgesics during the procedure, the total dose of analgesics postoperatively, postoperative shoulder pain, total intraoperative blood loss, operating time, postoperative nausea, time to first *postoperative* antiemetic, total dose of antiemetics postoperatively, and postoperative RASS scores (Richmond Agitation Sedation Scale)

3.0 BACKGROUND AND RATIONALE

3.1 Minimally invasive robotic surgery

Minimally invasive robotic surgery has myriad benefits over traditional open surgical techniques including reduced postoperative pain, shortened hospital stay, improved patient satisfaction, and improved cosmetic results[1]. Compared to laparoscopic surgery, robotic surgery has the additional benefit of improved surgical exposure and greater range of motion of instruments[1]. Robotic surgery has gained traction as a preferred surgical technique and continues to expand into all surgical subspecialties[2]. During robotic surgery, the abdomen is insufflated with carbon dioxide to generate a pneumoperitoneum for improved visibility of the abdominal compartment and organs. Unfortunately, the elevation in intra-abdominal pressure from CO_2 insufflation has untoward effects on hemodynamic stability and pulmonary mechanics. Equally important are the perioperative sequelae of elevated IAP.

3.2 Hemodynamic and cardiopulmonary changes associated with increased abdominal insufflation

As the abdomen is distended with carbon dioxide, physiologic derangements begin to be realized. An abundance of medical literature has been dedicated to evaluating and demonstrating the benefit of lower IAP over higher IAP. One study found a negative linear relationship between rising IAP and carotid artery blood flow, for example[3]. This study also found a negative exponential correlation between rising IAP and renal cortical blood flow[3]. Other studies have supported the inverse relationship between IAP and renal blood flow[4]. The effects on pulmonary mechanics have been widely reported and include decreased oxygenation, pulmonary compliance, and Functional Residual Capacity (FRC) and an increased peak airway pressure, and intrathoracic pressure[5]. The preservation of better pulmonary mechanics by reducing IAP is well understood and reported in medical literature[6, 7]. Deleterious cardiac effects of elevated IAP include increased afterload, mean arterial pressure (MAP), and systemic vascular resistance (SVR) with a decrease in stroke volume and cardiac output[5, 8]. Decreases in splanchnic blood flow have similarly been reported[9].

3.3 Elevated IAP and its sequelae

The hemodynamic and cardiopulmonary changes associated with increased abdominal insufflation have been implicated in a host of postoperative complications[10]. For example, elevated IAP has been implicated in the 40% incidence of atelectasis after laparoscopic surgery[11, 12]. Other postoperative complications including

respiratory failure, myocardial infarction, impaired oxygenation, and postoperative pain are suggested to be partially related to the hemodynamic and cardiopulmonary changes associated with increased abdominal insufflation[12, 13].

Because of these hemodynamic perturbations and their potential negative impact on patient wellbeing, international guidelines encourage the use of "the lowest IAP that will allow adequate exposure of the surgical field in place of a routine IAP"[14]. On the other hand, a valid argument against this recommendation is that surgeons will perform more precisely and efficiently with a better exposed surgical field[15]. With increased IAP the surgical field is better exposed giving surgeons a better visualization of the surgical field[16]. Perioperative clinicians must balance the risks and benefits of raising the insufflation pressure in the abdominal compartment. Given the widespread impact of elevated IAP on perioperative morbidity, it is incumbent on clinicians to investigate possibilities to reduce IAP. The investigators on this study are interested in exploring whether deep NMB will result in better visualization and lower IAP[17].

3.4 Neuromuscular blockade, IAP, and other outcomes

Muscle relaxation is a critical component during many surgical procedures and especially important for laparoscopic and minimally invasive robotic surgery[18]. King and colleagues demonstrated that routine use of NMB agents resulted in better operating conditions and a decrease in the incidence of unacceptable surgical exposure[19]. Improvement in surgical conditions and visualization is particularly important when a surgeon must operate in narrow spaces or in an enclosed abdominal compartment as is the case during robotic prostatectomy.

Some have argued that deep NMB (defined as train-of-four (TOF) values of zero (0) and post tetanic count (PTC) of 1-2) will further improve operating conditions[20]. Unfortunately, using deep NMB may be associated with complications including long-reversal times, incomplete recovery of neuromuscular function, which compromises respiratory and upper airway function, or the return of NMB after a period of normal neuromuscular function (recurarization)[21]. These complications stem from the traditional use of neostigmine/glycopyrrolate reversal which non-specifically increases acetylcholine availability at the neuromuscular junction.

Despite the reported benefit of deep NMB in mitigating the need for increased IAP to optimize surgical exposure, anesthesiologists have been limited in their ability to provide deep NMB during surgery[22, 23]. This is primarily because of the risk of residual paralysis in patients for whom deep NMB was utilized[24, 25]. Conventional practice attempts to balance the need to provide optimal surgical conditions and exposure with the risk of residual paralysis at the conclusion of surgery[25].

Because of the pharmacokinetics of neuromuscular blockers, deep NMB would not have been reversible in patients under such treatment in the past . Nowadays, sugammadex allows rapid reversal of deep NMB. Sugammadex is a modified cyclodextrin, specifically designed to bind free plasma molecules of the circulating neuromuscular blocking agent rocuronium[26]. With the introduction of sugammadex into daily practice, the risk of residual weakness after surgery is now equal for patients receiving deep or moderate NMB , and it is well recognized that deep NMB no longer carries its historical high risk of residual paralysis[27]. Unlike neostigmine/glycopyrrolate reversal, sugammadex is used exclusively with rocuronium due to its high specificity for this NMB agent. The combination of rocuronium and sugammadex makes it possible to achieve deep NMB and further improve surgical conditions in minimally invasive robotic surgery without the fear of prolonged reversal times or incomplete recovery of neuromuscular function[28].

Despite recent advances that have increased the safety of NMB, research on the association between the depth of NMB and surgical conditions has been limited and findings have been controversial. Some studies have shown that deep neuromuscular blockade during laparoscopic surgery may result in decreased postoperative pain and lower IAP[25, 29-32]. This is suggested to be primarily because the added relaxation

provides better intra-abdominal exposure resulting in less need for large abdominal insufflation[17, 29, 33, 34]. On the other hand, an equal number of studies have been unable to demonstrate a convincing decrease in postoperative pain with increasing depth of neuromuscular blockade[18, 35].

3.5 Why Robotic prostatectomy?

Robotic surgery is used in many surgical subspecialties including gynecology, urology, thoracic, and orthopedics. In our study, we will limit observations to robotic prostatectomy. Using the Nationwide Inpatient Sample (NIS), Hu et al. showed that minimally invasive robotic prostatectomy was associated with decreased length of stay, blood transfusion requirement, complication rate, and overall mortality compared with radical prostatectomy[10, 36]. As a result, a shift in practice patterns has made the robotic approach the most practiced technique in the United States for prostatectomy[10]. Over 60% of all prostatectomies were performed utilizing the robotic technique in 2007 and in the last decade, that number has steadily grown[1].

Robotic prostatectomies are the most common of all robotic procedures and are performed at all major medical centers in the US. Given the omnipresence of these procedures, findings from this study will resonate because of their broad appeal and generalizability. Focusing the study only on one type of surgery (as opposed to all robotic procedures) , will allow us to restrict inherent bias that could be introduced in comparing different surgical procedures. Carrying a study on a wide range of robotic surgeries might subject some patients to nuanced pathophysiological derangements and techniques such as varying number of insertion ports; need for greater pneumoperitoneum to expose different anatomical sites; and challenges that are disease-specific in the recovery period.

The National Surgical Quality Improvement Program (NSQIP) database reports a combined incidence of major postoperative complications of 5% after robotic prostatectomy. Among these complications are cardiovascular 0.37%, respiratory 0.47%, DVT or PE 0.82%, and renal failure 0.59%[10]. Robotic prostatectomies are a field that maintains a stubbornly high postoperative complication rate despite advances in techniques and perioperative care. Given the potential beneficial impact of reducing IAP in this patient population, and the likely benefit extended to other minimally invasive procedures with abdominal insufflation, it is imperative that investigators explore possibilities to reduce IAP.[5]

As mentioned above, there are a limited number of studies, with contradictory findings, that address the benefits of deep NMB in patients undergoing laparoscopic surgery. There are no similar studies found in the literature that evaluate these potential benefits in robotic surgery. Thus, the importance of our study is two-fold: it is essential to conduct a well designed to study to further corroborate any potential benefit of deep NMB as a generalizable technique, and it is essential to generate high-quality RCT that specifically focus on robotic surgery due its intrinsic differences with laparoscopic surgeries:

1) Robotic surgery affords a 3 dimensional view vs. a 2 dimensional view during standard laparoscopy
2) During robotic surgery, the surgeon is in direct control of the camera as opposed to standard laparoscopies, where an assistant holds the camera, which may restrict the surgeon’s optimal field of view.
3) The instruments are held by hand during standard laparoscopy in contrast to robotic surgery where the instruments are hed by a machine
4) During robotic surgery, the arms have “articulating” connections and can perform much higher order movements such as “wristing”.
5) The robotic systems can smooth out levels of force applied by the surgeon, an action known as scaling.
6) The robotic systems can remove random movements such as tremors resulting in a smooth, consistent and precise movement by the mechanical arms [37-39].

These critical differences directly affect the visualization of the surgical field and affect the requisite level of abdominal insufflation and IAP. Studies have shown variable requirements for abdominal insufflation in robotic compared to laparoscopic surgery[14, 37, 40].

Finally, robotic surgery is an avant-garde field that has quickly gained traction as a preferred surgical option. For many surgeries, including radical prostatectomy, robotics has surpassed standard laparoscopy in surgical volume. It is imperative we investigate robotic surgery specifically because there may be unknown factors that mitigate or contribute to the outcomes of interest.

3.6 Exploratory measures

Besides the marked hemodynamic perturbations realized during elevations in IAP, there are other factors that may affect the patient in the perioperative period. These effects have been shown to worsen with increasing IAP and include worsened postoperative shoulder tip pain, and greater postoperative nausea[34, 41-45]. In this study, the investigators will record these data points to determine whether deep NMB and IAP are associated with decreased shoulder tip pain or nausea. Conversely, elevated IAP has been shown to result in decreased operating times (secondary to improved exposure and more efficient technique)[42]. Elevated IAP also has a purported benefit of decreasing intraoperative bleeding by applying elevated pressures against bleeding vessels and tamponading blood flow[46, 47]. The association between IAP/NMB and blood loss and operating times will be explored[48]. All of these outcomes will be investigated as secondary endpoints of this study

3.7 Area under the curve (AUC)

AUC is a useful clinical endpoint for the aggregate effect over time and can summarize the average response to treatment over the period of observation. AUC is an appropriate summary measure for data collected over time, and it is commonly seen in pain measurements, as well as chronic obstructive pulmonary disease (COPD), diabetes, and pharmacokinetics studies[49-51]. For this study, we will use the AUC of patient-reported pain numeric pain scale (NPS) scores during the first postoperative hour as a measure for our first primary endpoint and area under the IAP curve during insufflation as a measure for our second primary endpoint. The numeric pain scale (NPS) is a subjective measure which can be used in recovery rooms to assist in the assessment of pain. Individuals rate their pain on an eleven-point scale. The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain).

3.8 Improving patient care

The volume of minimally invasive robotic surgeries - more specifically robotic surgeries - has increased exponentially in recent years. In fact, robotic prostatectomy is among the highest volume procedures at MSKCC. Despite recent advances in workflow and quality initiatives to improve patient care and outcomes, postoperative pain remains among the greatest complaints for patients undergoing robotic prostatectomy. A recent study utilizing a “recovery tracker” program at the Josie Robertson Surgery Center revealed an alarmingly high patient-reported pain scores. Of 177 patients who underwent robotic prostatectomy and were evaluated for postoperative pain, 49 reported VAS values of 5 or more. This translates to approximately 30% of patients reporting higher than moderate pain (Figure 1). It is worth stating that the recovery tracker collects information from patients who have already been discharged. Thus, these pain scores are not on the immediate postsurgical period.

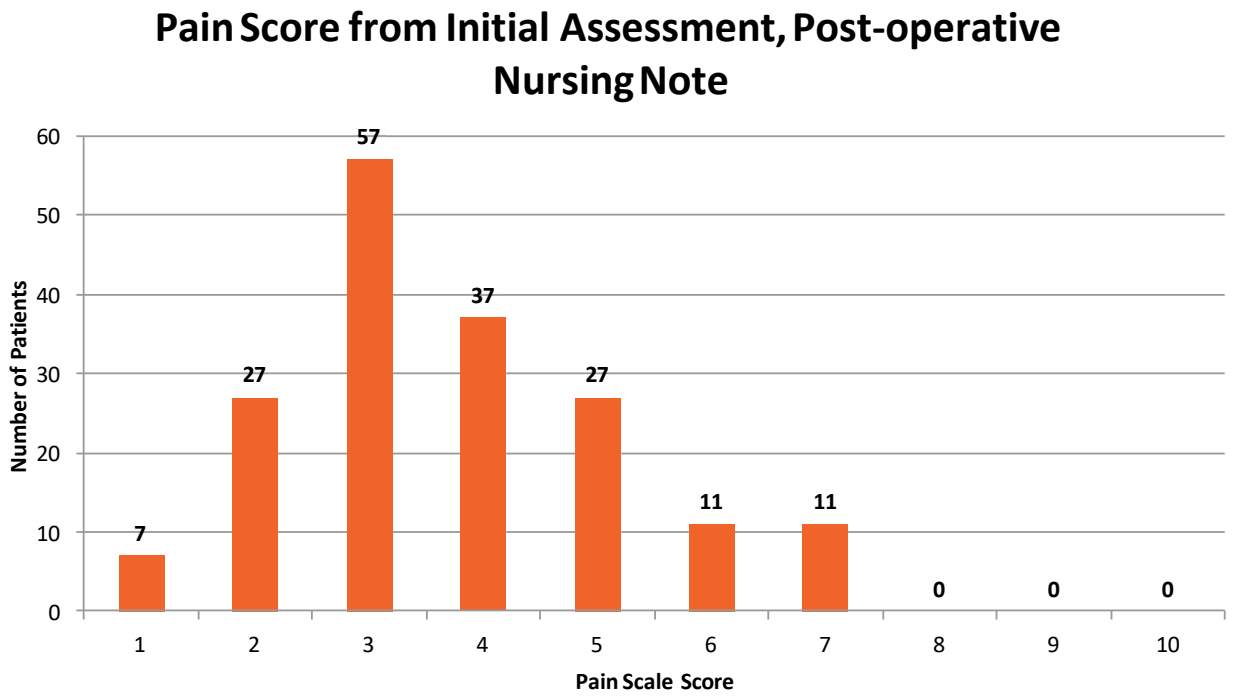


Figure 1. Patient-reported pain scores following robotic prostactectomy.

Pain in the immediate postsurgical period was measured in a recent pilot study. Investigators evaluated VAS pain scores for the first six postoperative hours in 37 patients undergoing robotic prostatectomies between January and March 2018. The results revealed a median VAS score of 4 (25^{th}, 75^{th} percentile : 3, 5) which represents moderate pain on the original scale, and mean of 1.3 (SD=0.5) on the natural log transformed scale. This preliminary evidence shows a high incidence of moderate to high pain score not only shortly after surgery, but also several days post discharge. For this reason it is incumbent on perioperative clinicians (i.e. anesthesiologists) to evaluate and consider any intervention that may lessen the pain burden of patients undergoing these procedures.

Summary

Because of the limited number of studies, the true impact of deep NMB on postoperative pain and IAP remains unresolved. Focused clinical trials are required so clinicians can improve patient care and recovery using approaches based on high quality evidence. This is of particular interest to robot-assisted surgery because even with the explosive increase in robotic surgery volume, the effects of deep NMB on these surgical conditions have never been studied[35, 52].

In this study, our first primary endpoint is to compare the effects of deep (intervention) vs. moderate (control) NMB on postoperative pain on patients undergoing robotic prostatectomy. Addtionatlly, since during robotic surgery, the abdominal IAP is controlled by the surgeon, we hypothesize that with deep NMB the surgeon will accomplish improved surgical exposure and will tolerate lower IAP[20]. Thus, our second primary endpoint is to investigate if surgical IAP levels will be different when a moderate or a deep NMB technique is used. Secondary endpoints will include evaluation of surgical operating conditions (as assessed by the Leiden scale) and the impact of deep NMB on post-op shoulder pain, post-op nausea, blood loss, and operating time.

At MSK we find ourselves in a priviledged position because we have the capability to handle large volumes of patients and operate with state of the art equipment; clinicians at MSKCC practice with an ethical commitment to generate high quality RCTs.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Study Design:

This is a single center, prospective, randomized controlled trial. The study protocol will receive IRB approval from Memorial Sloan Kettering Center Center. Written consent will be obtained from all patients who participate.

A total of 130 patients will be randomized to two groups—deep (interventional) or moderate (control) neuromuscular blockade, with 120 expected to be evaluable for each of the two primary endpoints. All patients enrolled will have surgery at Josie Robertson Surgical Center.

Intraoperative monitoring:

All patients will be monitored intraoperatively with routine monitors for oxygenation, ventilation, circulation, and temperature without deviating from standard American Society of Anesthesiologist (ASA) practice. This includes EKG, direct blood pressure, heart rate, oxygen saturation, end-tidal carbon dioxide, and temperature monitoring. Routinely, a TOF hand-held monitor is used for monitoring neuromuscular blockade. However, in this study, all enrolled patients will be monitored using a GE Anandic NMT device. The GE Anandic NMT is a FDA approved device being strictly used for this protocol on loan from GE Healthcare. The device is being used as indicated and will be utilized by a trained investigator. Members of our department have the expertise required for this device, which generates an electrical stimulus to the ulnar nerve and measures contractions of adductor pollicis muscle through a sensor attached to the tip of the thumb. A computer-generated TOF will eliminate observer variability in measuring TOF (see Appendix 8). TOF will be monitored every minute and recorded in the Electronic Medical Record. If the NMT monitor fails or cannot capture a baseline value, the patient will fall off protocol and clinician will be relegated to using a hand-held twitch monitor. However, this is an unlikely event and has not been reported during the pilot of this protocol.

Standardization of Anesthetics:

General anesthesia will be induced as per department routine with minimal variation on induction and maintenance of anesthesia. Upon arrival to the operating room (OR), standard ASA monitors will be applied before induction of anesthesia. All patients will be induced with midazolam (2 mg), propofol (2 mg/kg), fentanyl (1 mcg/kg), lidocaine (1mg/kg), and rocuronium (0.45 mg/kg). This anesthetic regimen will be standardized for both the moderate (control) and deep (intervention) NMB arms.

Patients will receive 100% oxygen during induction of anesthesia. After induction, anesthesia will be maintained at an age-adjusted minimum alveolar concentration (MAC) of 1 with sevoflurane. This will be titrated to maintain a Bispectral index of 35-55. Ventilation will be maintained with tidal volumes of 7 ml/kg, FiO2 less than 50%, and positive end-expiratory pressure (PEEP) and respiratory rate aimed towards normocapnia (ETCO2 of 35-45). For all patients in both arms of the study, two antiemetics (Dexamethasone 4 mg and Ondansetron 4 mg) as well as intravenous acetaminophen (1000 mg) will be administered.

Patients with rapid sequence inductions with succinylcholine will be excluded from participation. If a rapid sequence induction is conducted with rocuronium, the patient will have to demonstrate the start of recovery

even if the rocuronium dose exceeds 0.45mg/kg. The first sign of the start of recovery from neuromuscular blockade is defined as either the presence of a single twitch on TOF, or a post tetanic contraction of 1 or higher.

Maintenance and reversal of Neuromuscular blockade:

The TOF will be monitored continuously every minute after induction of anesthesia. Patients will be paralyzed with an 'intubating dose' of rocuronium (0.45 mg/kg) prior to intubation. At the first sign of start of recovery from neuromuscular blockade, rocuronium infusion will be started with either the control or interventional dose: 0.003 mg/kg/min (or 0.18mg/kg/hr) for moderate blockade and 0.006mg/kg/min (or 0.35mg/kg/hr) for deep blockade. The first sign of the start of recovery from NMB is defined as either the presence of a single twitch on TOF, or a post tetanic contraction of 1 or higher. It is possible patients will have spontaneous recovery and the return of TOF before incision due to the time needed for positioning and preparing of equipment. Infusion will be started at the first sign of return to TOF.

The infusion rate will be increased or decreased according to the scheme shown in Appendix 4. Adjustments to infusion rate will be done every 5 min until target TOF is achieved.

The Moderate NMB group (Control) will have rocuronium infusion titrated to moderate paralysis defined as TOF of 1-2 (infusion start rate 0.003mg/kg/min or 0.18mg/kg/hr).

The Deep NMB group (Intervention) will have rocuronium infusion titrated to deep paralysis defined as PTC of 1-2 (infusion start rate 0.006mg/kg/min or 0.35mg/kg/hr).

Muscle relaxation will be maintained until abdominal fascia closure, defined as when abdominal incision openings for all port sites are surgically closed. At this point, all patients will be reversed using sugammadex per manufacturer's dosing recommendations: for TOF greater than 2, administer 2 mg/kg; for PTC greater than or equal to 1, administer 4 mg/kg; for PTC of less than 1, investigators will wait until PTC count recovers to 1 and then give 4 mg/kg. . More detailed recommendations are outlined in Appendix 5.

In keeping with pharmacokinetic recommended dosages and infusion rates, all dosages and infusion rates are based on the patient's actual body weight.

Patient position:

All patients will be in supine position throughout surgery including induction and emergence of anesthesia. During surgery, all patients will be in steep Trendelenburg at 28 degrees, which is standard for all robotic prostatectomies. This position has been established as optimal for current robotic prostatectomies from the standpoint of the surgical visualization and cardiopulmonary effects intraoperatively[54]

Blinding:

Surgeons, patients and those assessing endpoints will be blinded to group assignment. For both arms of the study, black tape will conceal the IAP, so surgeons remain blinded to IAP value throughout the procedure. OR nursing routinely makes adjustments (increase/decrease) at surgeon's direction. Consistent with usual operating room workflow, surgeons will neither adjust the IAP nor have direct visualization of the IAP monitor. The OR nurse will be coached before the procedure to give a scripted response to surgeon's IAP adjustment requests (see Appendix 6). If a surgeon requests notification of actual IAP value during a case, the surgeon will be reminded that the patient is on protocol and value cannot be revealed. Therefore, the starting IAP can be (and will be) adjusted by the surgeon if limitations in visualization will be perceived. If surgeons can assume the value will be either 8, 9, or 10, the possible range of 3 points will adequately blind surgeons for the purposes of this study. There are three timepoints where surgeons may request a specific IAP:

1) During initial trochar insertion and insufflation
2) During the deep venous catheter dissection
3) At conclusion of surgery during hemostasis confirmation

Only at these timepoints can surgeons request an exact IAP. At all other timepoints including immediately preceding and after these timepoints, surgeons will be unaware of IAP and will not be able to infer the IAP based on their request. Additionally, the IAP value will be re-adjusted to the same value as before the change by the surgeon for the above 3 timepoints.At the conclusion of surgery (surgery end time) the surgeon will be asked to give their best guess as to the arm to which the patient had been assigned. This data will be used to evaluate the efficacy of the blinding process.

IAP pressure:

IAP (mm Hg) during pneumoperitoneum will be recorded at 15-minute intervals. In addition, IAP will be recorded if there is a pressure change performed regardless of the 15-minute interval. This means, an IAP measurement will be recorded at least once every 15 minutes to ensure that all IAP measurements will be captured within 15 minutes of IAP change. During our pilot, IAP measurements were changed a median of 8 times during robotic prostatectomy.

IAP pressure maintenance:

After trocar insertion, the insufflation pressure will be set to a 'starting IAP' value. All cases will begin at this value, which will be less than 10 but above 8 mm Hg. To prevent surgeon bias in initial IAP, the surgeon will not be aware of the starting IAP value. In an effort to partially blind the surgeons to this value, only the range is listed in this protocol (8 to 10), the exact value will be kept private. The blinded start value will be the same for all patients throughout this study. This value will be recorded in the anesthesia record and in the Intraoperative Data Collection Sheet (Appendix 1) . As necessary, surgeons will request an increase in pressure to improve visualization. This increase will occur at surgeon's direction, and may increase and decrease per surgeon request with scripted responses from OR nursing (see Appendix 6). Surgeons will remain blinded to the IAP value throughout a case as the value will be concealed with black tape. All surgeon requests to vary IAP will be recorded independent of an actual change in IAP.

Surgeon assessment of surgical exposure/visualization:

Overall surgical conditions will be estimated by the surgeon at 30-minute intervals. Our pilot data revealed that the average robotic prostatectomy lasted 5.5 hours. The Leiden surgical rating will be used with a scale of 1-5: 1 being extremely poor conditions and 5 being optimal surgical conditions. This surgical rating scale is well-established for assessing surgeon visualization in laparoscopy[17],[22].

Estimated blood loss:

Estimated blood loss will be extracted from the electronic medical record (EMR).

Postoperative pain (primary endpoint) and postoperative shoulder pain (exploratory endpoint):

The numeric pain scale (NPS) is a subjective measure which can be used in recovery rooms to assist in the assessment of pain. Individuals rate their pain on an eleven-point numerical scale. The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain). Postoperative pain scores are assessed by PACU nurses according to the following scheme:

As per Post Anesthesia Care Unit (PACU) standard of care at Josie Robertson Surgery Center, the PACU nurses that have been trained by the PI and blinded to randomization will ask the patient to rate their pain. The actual question asked is, "on a scale from 0-10, where 0 is no pain and 10 is excruciating pain, please rate

your pain." The pain assessment is administered verbally. PACU nurses ask the patient to rate their pain utilizing the NPS scale. The PACU nurses will be evaluating and assessing pain per the Josie Robertson standard of care by using the Post Anesthetic Discharge Scoring Tool (see Appendix 8). Hour 1 pain scores will be captured from the nursing PACU electronic flowsheet.

Hour 6 and 12 pain scores will be captured in the research assessment form (see Appendix 2).

Most patients on this study will be discharged before 24 hours so assessment at the 24 hour and 48 hour time points will be completed via telephone by the research staff. In the event that the patient has not been discharged from PACU at 24 and 48 hours, the pain scores will be captured in person on the research assessment form.

The 24 and 48 hour time points will be recorded as close to 24 and 48 hours as possible with a +/- 8 hour window to allow for difficulties in reaching patient (see Appendix 2).

Postoperative shoulder pain will be defined at postoperative times of 1-hour, 6-hour, 12-hour, 24-hour and 48-hour on the research assessment form. A pain scale of 0-10 will be utilized (0 = no pain, 10 = worst pain imaginable)

PACU TIME is defined as time of patient arrival to PACU.

Additionally, the total dose of analgesics will be recorded during the intraoperative and the postoperative periods until patient discharge.

Chronic pain patients will be excluded from the protocol. Chronic pain patients are routinely identified by LIP in Presurgical Testing (PST) in advance of surgery. Chronic pain will be defined as a patient on a sustained-release opioid in the last 3 months. To address potential confounding due to a history of chronic pain, analyses of pain-related endpoints will include an adjustment for preexisting chronic pain (yes/no) as a variable.

Patients receiving suboxone will be excluded from protocol.

Postoperative nausea:

As per the standard of care at the Josie Robertson Surgery Center, the PACU nurses that have been trained by the PI and blinded to randomization will ask the patient to rate their nausea. The actual question asked is "on a scale of 0-10, where 0 is no nausea and 10 is the worst nausea imaginable, please rate your nausea." The nausea assessment will be administered verbally.

The PACU nurse will record postoperative nausea and vomiting (PONV) in PACU (one-hour post-extubation) and at postoperative times of 1-hour, 6-hour, and 12-hour on the research assessment form., The 24 and 48-hour time points will be completed via telephone by the research staff on the research assessment form if the patient has been discharged before these time points are assessed.

The Apfel 4 point scale for predicting postoperative nausea and vomiting will be used. This scale includes four predictors: female gender, history of motion sickness, nonsmoking, and use postoperative opioids[55]. As all patients in the protocol for robotic prostatectomy will be male, Apfel score will not exceed 3 in any patient. If patient received EMEND preoperatively, the patient will be included in study but the nausea data will be excluded. PONV will be assessed with a scale of 0-10 (0=no nausea and 10 worst nausea imaginable)

In addition, the total dose of rescue antiemetics in the postoperative period will be recorded.

RASS scores:
RASS scores will be assessed and collected verbally by the PACU nurse (Hours 1, 6, and 12 post-

operatively). Hour 24 will be collected by phone call. This data will be captured on the research assessment form (see Appendix 2).

4.2 Intervention

A total of 130 patients will be randomized into two groups: deep (intervention) vs. moderate (control) blockade, with 120 patients expected to be evaluable for each of the two endpoints

General anesthesia will be induced as per department routine with minimal variation on induction and maintenance of anesthesia. Upon arrival to the operating room (OR), standard ASA monitors will be applied before induction of anesthesia. All patients will be induced with midazolam (2 mg), propofol (2 mg/kg), fentanyl (1 mcg/kg), lidocaine (1mg/kg), and rocuronium (0.45 mg/kg). This anesthetic regimen will be standardized for both the moderate (control) and deep (intervention) NMB arms.

Patients will receive 100% oxygen during induction of anesthesia. After induction, anesthesia will be maintained at an age-adjusted minimum alveolar concentration (MAC) of 1 with sevoflurane. This will be titrated to maintain a Bispectral index of 35-55. Ventilation will be maintained with tidal volumes of 7 ml/kg, FiO2 less than 50%, and positive end-expiratory pressure (PEEP) and respiratory rate aimed towards normocapnia (ETCO2 of 35-45). For all patients in both arms of the study, two antiemetics (Dexamethasone 4 mg and Ondansetron 4 mg) as well as intravenous acetaminophen (1000 mg) will be administered.

Level of the blockade will be monitored continuously with a TOF GE Anandic NMT device. All patients will be maintained in the same surgical position (angle of Trendelenburg) per robotic urological surgery standard. All surgeons will be blinded to the 'starting IAP' value and all procedures will begin at this value, In addition, IAP value will be recorded at 15-minute intervals. Changes in IAP outside the 15-minute interval measurement point will also be recorded. Increases or decreases in IAP of 1 mmHg per surgeon's request will be allowed throughout the case. Surgical exposure/visualization will be assessed at 30-minute intervals using the Leiden surgical rating scale of 1 to 5 (see Appendices 1 and 3).

Monitoring of neuromuscular block will be in accordance with GE quick guide (see Appendix 8) and it is briefly described below:
Properly secure the sensor of choice (as depicted in Appendix 8). Press measurement start-up.The monitor will start the measurement by setting the stimulus current automatically and by performing a reference measurement. This will be done during induction, before administration of any muscle relaxant. Depolarizing relaxants result in an equal drop in all four responses, without fade. Non-depolarizing relaxants cause a fade in the responses, indicated by a lower TOF% and a slope in the bar graph. Neuromuscular block Is used to facilitate endotracheal intubation. The anesthesia provider can use the time when all responses disappear (i.e., TOF Count is 0) as a guide to determine when to intubate. During surgery, TOF Count is used to maintain a steady optimal level of neuromuscular block. When TOF Count exceeds a level set by the user, the GE monitor will give a "Block recovery" message.

TOF monitoring will occur every minute during the procedure. This will allow for recovery at the neuromuscular junction after post-tetanic stimulation[56]. Administration of additional muscle relaxant will not be allowed. Patients will be maintained in their respective randomized groups (moderate versus deep) and treated unless a change or deterioration in the clinical condition requiring additional muscle relaxant occurs, at which point, such patient will be dropped from the study.

Muscle relaxation will be maintained until abdominal fascia closure, defined as when abdominal incision openings of all port sites are surgically closed. All patients will be reversed using sugammadex as per manufacturer's dosing recommendations: for TOF greater than 2, administer 2 mg/kg; for PTC greater than or equal to 1, administer 4 mg/kg; for PTC of less than 1, investigators will wait until PTC count recovers to 1 and then give 4 mg/kg.. More detailed recommendations are outlined in Appendix 5.

Current standard of care for patients undergoing robotic prostactectomy is moderate blockade (i.e. 1-2 twitches on TOF). Patients in either arm of the study will receive AT LEAST as much blockade as current standard of care. It is extraordinarily unlikely that surgical investigators in this study will demand deeper neuromuscular blockade than a moderate blockade. If a surgeon requests deeper blockade, they will be reminded that the patient is in protocol and that depth of blockade will be at least moderate blockade as per current standard of care.The surgeon will remain blinded to the depth of neuromuscular blockade. In the case a surgeon assesses that deeper blockade is necessary for a given patient, the anesthesia provider will give additional neuromuscular blockade.

Estimated blood loss and total surgical operative time will be extracted from Electronic Medical Record. Postoperatively, endpoints (pain and nausea) will be recorded on all patients by a PACU nurse according to pain and nausea scales. The 24 and 48-hour assessments will be captured via telephone by the research staff. [51, 57]

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Rocuronium use for muscle relaxation is standard during general anesthetics at MSKCC. Sugammadex while relatively new at our institution has been used with increasing frequency for various surgical cases. Robotic prostatectomies always require neuromuscular blockade. Patients will be receiving these agents whether or not they are involved in study.

Patients routinely receive varying dosages of rocuronium. There is no consensus on “optimal” dose of rocuronium or on “optimal” depth of neuromuscular blockade; given the underlying equipoise, the dosage will be determined based on the intervention arm of the study. Patients in the deep neuromuscular blockade arm will likely receive higher aggregate dose of rocuronium. This will pose no increased risk to patient given the ability to reverse both moderate and deep blockade with sugammadex. Furthermore, the higher dosages of rocuronium and sugammadex required in this protocol do not pose increased risk to patients. Studies have demonstrated that the incidence of adverse events in the dose groups described does not indicate a dose-response relation. [58, 59]

The only known drug interaction with sugammadex is Toremifene. Patients receiving Toremifene (anti-estrogen family of drugs) could cause a delayed recovery from neuromuscular blockade. Patients on Toremifene will be excluded from study (see Appendix 9).

Sugammadex safety in patients under the age of 17 has not been established. All patients in this study will be 18 years or older.

Sugammadex use for patients with severe renal impairment is not recommended. Patients with severe renal impairment (defined as creatinine clearance <30 ml/min) will be excluded from this study (see Appendix 9).

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Adult patients under the age of 80.
2. American Society of Anesthesiologists Physical Status 1, 2, 3.
3. Elective Robotic Prostatectomy.
4. Patient undergoing surgery at Josie Robertson Surgical Center

6.2 Subject Exclusion Criteria

1. Age younger than 18.

2. Inability to provide informed consent.
3. Allergy to rocuronium, sugammadex, midazolam, propofol, fentanyl, lidocaine, mannitol (IV Acetaeminophen), IV Acetaminophen, Ketorolac, Morphine, Hydropmorphone, Dexamethasone, Zofran, Bendaryl, Compazine
4. Neuromuscular disease.
5. Any patient with previous abdominal surgery less than or equal to 20 years prior to scheduled surgery date.
6. Patients with BMI> 35.
7. Severe renal impairment (creatinine clearance <30 ml/min).
8. Pt receiving Toremifene or any history of receiving Toremifene.
9. Chronic pain patients.
10. Patients receiving suboxone.
11. Patients receiving succinylcholine.

7.0 RECRUITMENT PLAN

All patients who meet all eligibility criteria and are scheduled for robotic prostatectomies performed by a surgeon listed on this protocol, will be approached to gauge interest in participating in the study.

All patients will undergo surgery at Josie Robertson Surgical Center. Potential patients will be identified by the study team ahead their scheduled preoperative visit. The study team will work closely with the urology clinic staff to ensure documents are prepared ahead of time.The consent discussion for this study will occur during the preoperative visit in the urology clinic by either the surgeon or the advanced practice provider (Nurse practitioners or physican assistants). The protocol will be described to all prospective patients by the consenting professional, who will obtain informed consent from agreeing patients. Interested patients who do not provide provide consent during their pre-operative visit will be followed up by the study team at another time prior to surgery if possible. All consent discussions will occur at least 1 day prior to the patient's surgery. There will be no compensation (financial or otherwise) to participants who enroll in the study. Accordingly, there is no direct benefit to patients who agree to participate in the study.

Surgeons involved in the study as investigators will receive a detailed fact card that will be used for their reference and to educate their patients. This fact card will include:

1. Background and rationale
2. Scientific aims
3. Intervention and treatment plan
4. Protocol summary
5. Contact information for PI, research study assistant

Educational program: Surgeons will receive orientation and education on all aspects of the protocol. The education sessions will first in a didactic group session one month before the start of enrollment, and followed by a one-to-one review session with the study PI one week before the start of enrollment to review details of the study.

Because of the nature of the surgical procedure, only men will be enrolled in the study. All male patients regardless of race and ethnic background will have equal opportunity to participate in the study.

To maintain uniformity in protocol execution, only the anesthesiologists and CRNAs listed as an investigator on the face sheet will be eligible to conduct the study cases.

8.0 PRETREATMENT EVALUATION

There is no need for additional pretreatment evaluation and participants in the study will not receive additional testing or evaluations.

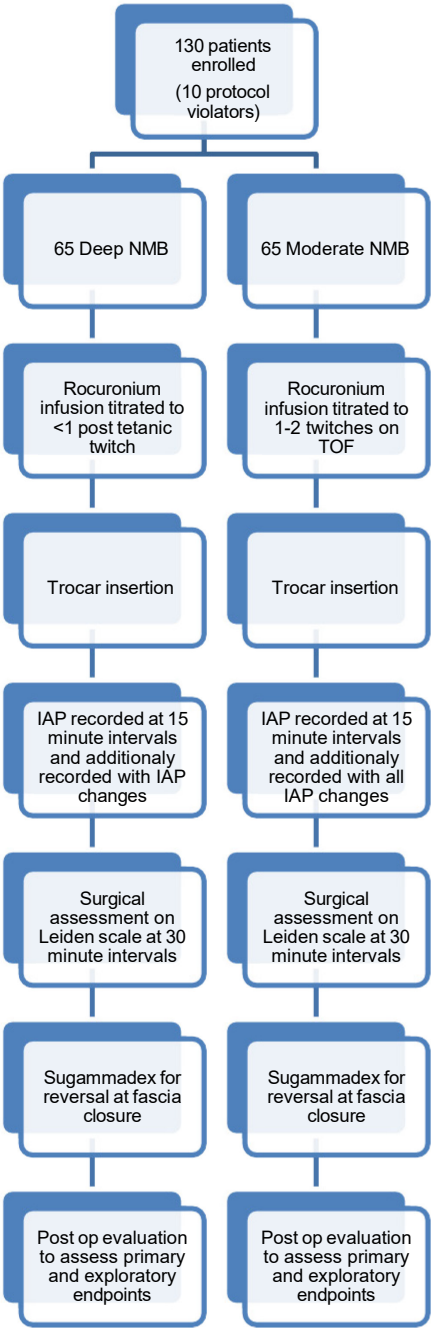
9.0 TREATMENT/INTERVENTION PLAN

A total of 130 patients scheduled for robotic prostatectomies will be randomized into two groups: deep (experimental intervention group) versus moderate (control) blockade, with 120 expected to be evaluable for each of the two primary endpoints. In both groups, anesthesia will be induced and maintained per our department's current routine, and standardization will is clearly defined previously in the protocol. For each patient in either arm of the study, recovery from induction dose of rocuronium will be established before re-initiating muscle blockade (deep versus moderate) with rocuronium infusion. Level of the blockade will be monitored continuously with GE Anandic NMT device and dose of rocuronium will be titrated.

All patients will be maintained in the same surgical position (angle of Trendelenburg) per robotic urological surgery standard. All surgeons will be blinded to the 'starting IAP' value and the IAP value will be recorded at 15-minute intervals. Changes in IAP outside the 15-minute interval measurement point will also be recorded. Increases or decreases in IAP per surgeon's request will be allowed throughout the case. Surgical exposure/visualization will be assessed at 30-minute intervals using the Leiden surgical rating scale of 1 to 5. Surgeons will be alerted if IAP reaches 15, which is the standard upper limit of IAP at MSKCC. Investigators request they know the IAP at a level of 15, so they can weigh risk/benefit of continuing to operate at that higher threshold of IAP. At the end of a case, patients in both arms will be reversed with sugammadex at fascia closure. Data will be collected from the of the surgical case. Patients who experience unexpected intraoperative events including death, conversion to open procedure, a decline in clinical condition that would end a planned procedure, anaphylaxis, or a life-threatening hypersensitivity reaction to any medication will be removed from the study.

Estimated blood loss will be recorded from Electronic Medical Record. Postoperatively, endpoints (pain and nausea) will be recorded on all patients by a PACU nurse and research staff(up to 48 hours postoperatively) according to pain and nausea scales as described above. The a PACU nurse will perform these assessments while the patient is on-site. The research nurse will complete 24 and 48-hour assessments by telephone.

10.0 EVALUATION DURING TREATMENT/INTERVENTION



11.0 TOXICITIES/SIDE EFFECTS

The most common adverse reactions are vomiting, low blood pressure, pain, headache, and nausea. Sugammadex (BRIDION) may temporarily reduce efficacy of hormonal contraceptives. Severe, potentially life-threatening allergic reactions were reported in clinical trials. The incidence of severe toxicities (i.e., anaphylaxis) is estimated at 29 per million cases[60]. In a systematic review of hypersensitivity associated with

sugammadex administration in 2014 (Sugammadex has been available for clinical use in Europe since 2008), only 15 cases met inclusion criteria. Signs and symptoms include rash (12/15 cases) and World Allergy Organization anaphylaxis (11/15 cases). Other hypersensitivity reactions that can prove life-threatening in the presence of rash are hypotension, tachycardia, or decreased SpO2 in 60%, 53%, and 47%[61].

There have been cases of abnormally slow heart rate (bradycardia), some of which have resulted in cardiac arrest within minutes after the administration of Sugammadex.

Surgical complications will be recorded in a uniform, recognized method using CTCAE version 5.0 to report adverse events during study followup. Type and severity of adverse events will be recorded.

In addition, per MSKCC urology standard, complications will be recorded using the Clavien-Dindo Classfication system. The therapy used to correct a specific complication is the basis of this classification in order to rank complications in an objective and reproducible manner.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

IAP as an endpoint and outcomes assessment (surgeon visualization, estimated blood loss, surgical operative time, postoperative pain and nausea scores) will be as follows:

IAP pressure:

IAP (mmHg) during pneumoperitoneum will be recorded at 15-minute intervals, and IAP will be recorded at every pressure change performed even when a change occurs within 15-minute interval.

IAP pressure maintenance:

After trocar insertion, the insufflation pressure will be set to the 'starting IAP'. All cases will begin at this value, which will be greater than or equal to 8 and less than 10. Surgeons will be blinded to this value. As necessary, surgeons will request an increase in pressure to improve visualization. This increase will occur at surgeon's direction and may increase and decrease per surgeon request.

Surgeon assessment of surgical exposure/visualization:

Overall surgical conditions will be estimated by the surgeon at 30-minute intervals. The Leiden surgical rating scale will be utilized with a scale of 1-5. Where 1 is extremely poor conditions, and 5 is optimal surgical conditions. This surgical rating scale is well-established for assessing surgeon visualization in laparoscopy [17] [22].

Estimated blood loss:

Recorded from Electronic medical record

Postoperative pain (primary endpoint) and postoperative shoulder pain (exploratory endpoint):

The numeric pain scale (NPS) is a subjective measure which can be used in recovery rooms to assist in the assessment of pain. Individuals rate their pain on an eleven-point numerical scale. The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain).

Postoperative pain scores are assessed by PACU nurses according to the following scheme:

As per Post Anesthesia Care Unit (PACU) standard of care at Josie Robertson Surgery Center, the PACU nurses that have been trained by the PI and blinded to randomization ask the patient to rate their pain. The

actual question asked is, “on a scale from 0-10, where 0 is no pain and 10 is excruciating pain, please rate your pain.” The pain assessment is administered verbally. PACU nurses ask the patient to rate their pain utilizing the NPS scale..

The trained PACU nurses will be evaluating and assessing pain per the Josie Robertson standard of care by using the Post Anesthetic Discharge Score Tool (see Appendix 8).

Hour 1 pain scores will be captured from the Nursing PACU flowsheet.

Hour 6 and 12 pain scores will be captured in the research assessment form (see Appendix 2).

Most patients on this study will be discharged before 24 hours so assessment at the 24 hour and 48-hour time points will be completed via telephone by the research staff. In the event that the patient has not been discharged from PACU at 24 and 48 hours, the pain scores will be captured in person on the research assessment form.

Postoperative shoulder pain will be defined at postoperative times of 1-hour, 6-hour, 12-hour, 24-hour and 48-hour on the research assessment form. A pain scale of 0-10 will be utilized (0 = no pain, 10 = worst pain imaginable).

Additionally, the total dose of analgesics will be recorded during the intraoperative and the postoperative periods until patient discharge.

Chronic pain patients will be excluded from the protocol.

Postoperative nausea:

As per the standard of care at the Josie Robertson Surgery Center, the PACU nurses that have been trained by the PI and blinded to randomization will ask the patient to rate their nausea. The actual question asked is, “on a scale of 0-10, where 0 is no nausea and 10 is the worst nausea imaginable, please rate your nausea.” The nausea will be administered verbally.

The PACU nurses will record postoperative nausea and vomiting (PONV) in PACU (one-hour post-extubation) and at postoperative times of 1-hour, 6-hour and 12-hour, on the research assessment form. The 24 and 48-hour time points will be completed by the research staff on the research assessment form via telephone if the patient has been discharged before these time points are assessed.

The Apfel 4 point scale for predicting postoperative nausea and vomiting will be used. This scale includes four predictors: female gender, history of motion sickness, nonsmoking, and use postoperative opioids[55]. As all patients in the protocol for robotic prostatectomy will be male, Apfel score will not exceed 3 in any patient. If patient received EMEND preoperatively, the patient will be included in study but the nausea data will be excluded. PONV will be assessed with a scale of 0-10 (0=no nausea and 10 worst nausea imaginable)

In addition, the total dose of rescue antiemetics in the postoperative period will be recorded.RASS scores will be assessed and collected verbally by the PACU nurse (Hours 1, 6 and 12 post-operatively); Hour 24 will be collected by phone call. This data will be captured on the research assessment form.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Criteria for removal of subject from the study will include patient death, surgical conversion from robotic to open procedure, intraoperative deterioration in clinical condition that would end a planned procedure.

Patients are considered evaluable for the first primary endpoint (IAP) if they can provide at least one IAP recording; patients are considered evaluable for the second primary endpoint (Pain) if they can provide at least one NPS pain score within 6-hours after surgery. Study data will be analyzed according to a modified intention-to-treat principle ("modified" because patients considered inevaluable for a given primary endpoint will be excluded from the analysis of that endpoint).

The following are a list of possible perioperative scenarios. We expect these to occur extremely infrequently. We anticipate fewer than 10 occurrences during the study period and have planned the protocol accordingly.

1) *Cancelled surgery*
   Patient will not provide either primary endpoint therefore patients in this category will be excluded from primary analysis

2) *Patient death*
   For patients who die in the perioperative period, any data up until patient death will be analyzed.
   These patients may possibly contribute data for only one of the two primary endpoints (IAP)

3) *Surgical conversion from robotic to open procedure*
   Any data up until conversion will be analyzed.
   These patients may possibly contribute data for only one of the two primary endpoints (IAP)

4) *Intraoperative deterioration in clinical condition that would end planned procedure*
   For patients who experience deterioration in clinical condition that ends planned procedure, any data up until deterioration will be analyzed.

   However, there will be an investigation to assess the possible (but extraordinarily unlikely) influence of protocol in leading to deterioration.

5) *Deviation from protocol by giving additional dose of NMB to satisfy surgeon request for better visualization*

   All data in this scenario will be analyzed.. Secondary analysis will be conducted as treated.

6) *Equipment failure of the neuromuscular train of four monitoring device*
   Any data up until failure of neuromuscular train of four monitoring device will be analyzed.patient will be considered evaluable for only one of the two primary endpoints (IAP).

7) *Accidental unblinding of surgeon*
   All data will be analyzed.. This will be an evaluable patient.

8) *Accidental unblinding of investigator conducting postop evaluation*
   All data will be analyzed. This will be an evaluable patient.

9) *Accidental unblinding of patient*
   All data will be analyzed. This will be an evaluable patient

10) Monitoring issues

TOF data measured on the GE NMT monitoring device, which currently uses GE's old algorithm, will be sent to GE without randomized arm information to derive corrected TOF (TOFc) based on GE's proprietarty new algorithm. Per correspondence with Mika Sarkela, PhD, Principal Engineer at GE Healthcare, he states, "We have made improvements to the TOF algorithm, as its limitations are well known and published[64]. Whereas the old TOF algorithm counted twitches based on their magnitude only, the new algorithm takes both the magnitude and the fade into account. The new algorithm is not published yet and will be in the next Carescape monitor release." Patients with substantial disagreement between TOF and TOFc measurements will be considered as having monitoring issues. Agreement is defined by the proportion of measurements that are perfectly aligned between TOF and TOFc. A second definition for agreement will be the proportion of measurements with a TOF and TOFc difference of <2 twitches. Cases with agreement <80% will be considered a substantial disagreement. We may consider a more stringent threshold for substantial disagreement, for example, agreement <90%.

In addition to those with substantial disagreement between TOF and TOFc (described above), the following patients will also be identified as having monitoring issues:

1. Patients with bedside TOF measurements in the operating room but no TOF data available for correction to TOFc
2. Patients with incorrect stimulus electrode placement determined by saved images reviewed by GE

Patients with monitoring issues have TOF measurements with varying levels of noise interference, which distinguishes them from patients with, "6) Equipment failure of the neuromuscular train of four monitoring device," which have no TOF measurements. All patients with monitoring issues will be included in the intention-to-treat analyses. Additional analyses based on monitoring issue status are summarized in section **14.0** Study participants that meet the removal criteria above will have their cases reviewed. These cases will be reviewed by an independent panel of surgical and anesthesiology investigators to ensure that the event is not associated with or caused by visibility during the surgery prior to their removal from the study. Any event determined to be due to visibility will be reported to IRB.

14.0 BIOSTATISTICS

In this single-blinded prospective randomized study, patients will be randomized in 1:1 ratio to two arms: moderate NMB (control) or deep NMB (intervention). The two primary endpoints of interest in this study are: levels of IAP and postoperative pain. Thus, in the sample size calculation below, we consider multiple primary endpoints and power the trial to detect success in at least one endpoint. The first primary endpoint of interest is IAP. The second primary endpoint of interest is Pain scores within 6-hours post operation. To characterize the entire set of a patient's IAP measurements under insufflation, we consider the use of area under the curve (AUC). We plan to randomize 130 patients to moderate or deep NMB arms, stratified by BMI (< vs >=30) and surgeon, and expect 120 patients to be evaluable for each of the two primary endpoints. Patients are considered evaluable for the first primary endpoint (IAP) if they can provide at least one IAP recording; patients are considered evaluable for the second primary endpoint (Pain) if they can provide at least one NPS pain score within the 6-hours postoperation.

AUC is a useful clinical endpoint for the aggregate effect over time and can summarize the average response to treatment over the period of observation. AUC is an appropriate summary measure for data collected over time, and it is commonly seen in pain measurements, as well as chronic obstructive pulmonary disease (COPD), diabetes, and pharmacokinetics studies[49-51]. For this study, we will use the area under the IAP curve during insufflation as a measure for the first primary endpoint which focuses on the effect of deep NMB on IAP during robotic prostactetcomy. We will consider the time-weighted measure of AUC that integrates serial

assessments of the patient's IAP measurement over time using the trapezoidal rule. The corresponding "mean AUC" (AUC_{mean}) is obtained as AUC/duration of insufflation for each patient. From **Kim et al**, mean IAP decreased by approximately 22% (standard deviation [SD] = 1.3) from moderate NMB to deep NMB.[29]

For the second primary endpoint based on postoperative pain, we will collect all NPS pain scores within the 6-hours postoperation and will express results as AUC_{pain} at the patient level. In a retrospective analysis of 37 patients from a similar population (See Section 3.8), mean pain level within the 6-hours postoperation was 1.3 (SD of 0.5) on the **log-transformed NPS scale**.

Sample size calculation is based on the mean AUC_{IAP} and AUC_{pain} within 6-hours postoperation across patients in each arm. We power this study with 2 primary endpoints to detect 20% decrease in IAP (from 13.9 to 11.1, SD of 4) and 25% decrease in pain scores within the 6-hours postoperation (from 1.3 to 0.975; SD of 0.5) with deep vs moderate NMB, with type I error rate of 0.025 for each endpoint. The change in NPS scores (25% or 1 point on the raw scale) is a validated clinically meaningful change[62, 63]. The decrease in pain scores on which the sample size estimate is based on the **natural log transformed scores**. This calculation assumes independence of the two primary endpoints. We elected to increase the standard deviation of the AUC_{IAP} in this power calculation as a conservative measure because the population from the reference study is different from the population of interest. A total of 120 patients evaluable for each of the primary endpoints will provide 90% power to detect a significant difference in **at least one of the two endpoints**. This sample size also allows for an interim analysis halfway through enrollment, using O'brien-Fleming boundaries with Lan de Mets spending functions for futility. We base the interim analysis decision rule on both of the primary outcomes. The trial will continue to full enrollment if the interim analysis results for either/both of the primary outcomes reports $p<0.755$. The trial may be terminated if $p>0.755$ for both outcomes. We will conclude that the arms are significantly different if $p\leq0.025$ for either of the outcomes. In order to ensure at least 120 patients evaluable for each of the primary endpoints, we plan to randomize at least 130 patients (See Section 13.0 for potential perioperative scenarios).

Analysis of the primary endpoint which involves IAP will be AUC_{IAP} compared between the two arms using the linear mixed-effects model: randomized arm as the fixed-effect, BMI as the adjustment covariate, with surgeon-level random effects. Transformation of the outcome may be applied if the normality-of-errors assumption is violated. As a secondary analysis, the longitudinal IAP measurements will be analyzed using linear mixed-effects models including time and randomized arm as fixed-effects with stratification variable (BMI), and patient-level random effects, nested within surgeons. In the rare case that the patient's IAP is beyond 15 the surgeon will be unblinded to the IAP, and only the IAP up to the point of unblinding will be included in the analysis. 15 is the conventional goal for the upper limit of IAP at MSKCC. Investigators request they know the IAP at a level of 15, so they can weigh risk/benefit of continuing to operate at that higher threshold of IAP. In this rare occurrence, patients will still be included in the analyses as modified intent-to-treat, including IAP values until IAP-unblinding.

Analysis of the second primary endpoint will be AUC_{pain} within 6-hours postoperation. AUC_{Pain} analysis will be conducted with linear mixed-effect model with appropriate transformation for the outcome for normality. The model will include randomized arm as fixed-effects along with stratification variable (BMI), and patient-level random effects, nested within surgeons.

For the primary analyses, all recorded IAP will be analyzed in a modified intent-to-treat fashion. Where a patient randomized to moderate NMB crosses over to deep NMB, all recorded IAP will be analyzed under the randomized arm. As a secondary analysis of the primary outcome, we will perform an as-treated analysis where the set of IAP values will be assigned to the actual intervention received. Correlation between AUC_{IAP} and AUC_{Pain} will be summarized using Spearman correlation coefficient. Additionally, the primary endpoints will be summarized between patients with and without neuromonitoring issues (see

Section 13.0). As a sensitivity analysis, planned analyses of both primary endpoints will be repeated after excluding patients with neuromonitoring issues (see Section 13.0).

Although the occurrence will probably be rare, accidental unblinding will be recorded as a protocol violation as part of standard reporting procedure. According to the ICH E9 Statistical Principles for Clinical Trials, usually of violations that occur post-randomization, it is appropriate to include the data from such subjects in the analysis, consistent with the modified intention-to-treat principle. We will include these cases in the primary analysis of the primary outcome in the randomized arm. For each case of major protocol violation, we will enroll an additional patient randomized and included in the analyses. Also, we will perform per protocol analysis that excludes patients who had accidental unblinding.

Surgeon assessment of surgical conditions (continuous measure, on a 1 to 5 scale) recorded every 30 minutes, will be analyzed with linear mixed-effects models as above.

Estimated blood loss (EBL) will be compared between the two arms using linear mixed-effects model (randomized arm and BMI fixed-effects variables, and surgeon-level random effect), accounting for duration of surgery if necessary (i.e., rate of EBL). Transformation of the outcome may be applied if the normality-of-errors assumption is violated.

Postoperative pain (surgical and shoulder pain, 0 no pain to 10 worst pain imaginable), defined at postoperative 1-hour, 6-hour, 12-hour, 24-hour, and 48-hour post operation will be compared between the two arms using linear mixed-effects models with appropriate transformation for the outcomes for normality.

The model will include patient-level random effects (nested within surgeons), treatment arm, and time as fixed-effects, along with stratification variable (BMI) as adjustment factors. To address potential confounding due to history of chronic pain, patients with chronic pain will be excluded from protocol. Chronic pain will be defined as a patient on a sustained-release opioid in the last 3 months. Besides patient-reported pain scores, perioperative analgesia use will be analyzed similarly to the pain scores: intraoperative cumulative IV analgesia use will be compared between the two arms after adjusting for duration of surgery; while postoperative IV analgesia use will be analyzed as cumulative total dose within the first 6-hours post surgery and until prior to discharge (with adjustment for duration of postoperative stay in the analysis).

Postoperative nausea (measured at the same intervals) will also be analyzed with linear mixed-effects models. To address potential confounding due to preoperative risk for nausea, the model will include adjustment for preoperative Apfel score (4 point scale with a maximum of 3 points due to an all male patient population) and preoperative EMEND use. In addition to patient-reported nausea scores, postoperative antiemetic use will be analyzed in the following fashion: the use of any antiemetics will be analyzed with a mixed-effects logistic regression model, and the use of any antiemetics within the first 6-hours post surgery and until prior to discharge will be analyzed with linear mixed-effects models. Time to first rescue antiemetic medication will also be recorded and compared between the two arms using Kaplan-Meier approach and log-rank test.

We will assess the relationship between the treatment arms and operating time (defined as the time between incision to surgery end) using a linear mixed-effects model with transformation for the outcome for normality. The model will include treatment arm and stratification variable (BMI) and surgeon-level random effect

Richmond Agitation Sedation Scale (RASS) scores, measured at 1, 6, 12, 24 hours postperatively will be modeled and compared between the two arms using linear mixed-effects model. The model will include treatment arm and stratification variable (BMI) and surgeon-level random effect.

One primary concern from deep paralysis is postoperative pulmonary complications and the need for reintubation and prolonged postoperative intubation. All patients who receive neuromuscular blockade are at

risk of residual paralysis at the conclusion of surgery. Patients who experience residual paralysis from inadequate neuromuscular blockade may experience postoperative pulmonary complications such as respiratory distress, aspiration, and pneumonia, ultimately requiring reintubation and prolonged postoperative intubation. The likelihood of respiratory complications and risk for reintubation are not expected to be different between the two arms. ***This risk is independent of the dose or timing of rocuronium administration.*** NSQIP data reported 0.82% respiratory complications and 0.47 pulmonary emboli/DVT for 1.29% complication risk from postoperative pulmonary complications[37]. If one or more patients requires reintubation, experiences respiratory distress, aspiration or pneumonia among the first 45 elligible patients (≥2.2% incidence rate) regardless of treatment arm, the trial will be paused for the investigators to assess whether the complication was attributable to the intervention prior to restarting the trial. The incidence of 30-day postoperative pulmonary complications will be recorded and summarized by treatment arm. Postoperative pulmonary complications for recording are defined as the need for reintubation, respiratory distress, aspiration, and pneumonia.

For descriptive purposes, we will assess andthe accuracy of surgeon's best guess as to which arm a given patient was assigned. This will allow us to assess blinding success. Similarly, all requests by surgeon to change IAP intraoperatively will be recorded and summarized separately by arm using descriptive statistics.

Reintubations will be limited to any intubation that occurs within the first 24 hours postoperatively.

Respiratory distress is defined by tachypnea to a respiratory rate greater than 30, OR desaturation of 10% or greater from baseline spO2. (either criterion alone will satisfy definition)

Aspiration is defined by pharyngeal or gastric contents below the vocal cords. This must be confirmed by suctioning of pharyngeal or gastric contents from the trachea, fiberoptic bronchoscopy or the finding of a new infiltrate on CXR within 24 hours postop.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will have to complete a protocol-specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

The study will be conducted in a prospective randomized fashion. We plan to randomize 130 patients in 1:1 ratio to ensure at least 120 patients would be evaluable for each of the two primary endpoints. During the registration process, research staff will complete a protocol-specific Eligibility Checklist. After consent is obtained and eligibility is established, patients will be registered as described in Section 15.1.

After successfully registering the subject, the research study staff will randomize them in CRDB (Clinical Research Database) stratified by BMI (<30 vs ≥30) and surgeon. Only the anesthesia research team (CRM and CRCs) and the anesthesia care team in the OR will have access to the arm assignments.

16.0 DATA MANAGEMENT ISSUES

A clinical research coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, patient registration, assistance with data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization and coordination of the activities of the protocol study team. The CRC will be integrated into current weekly and monthly meetings where complications are recorded, procedures reviewed and outcomes documented. The PI will personally meet with the CRC on a weekly basis to assist with and review the collection and entry of data.

All data collected will only be used for the study.Data points will be collected using iCollect software that will be provided by the sponsor.The iCollect software will be on a MSKCC verified workstation laptop that is approved by MSKCC Information Security. It will be maintained in a confidential clinical research database by research study personnel only under the direct supervision of the principal investigator. Data collected for this study will be entered into and managed via a secure REDCap Database. REDCap, Research Electronic Data Capture, is an open source platform that allows for the collection of research data in a secure manner over a web based interface. Usage of the platform is contingent on an open source license. The platform was developed by Vanderbilt University which MSK has a standing agreement with to allow the usage of REDCap for academic/research purposes.

For this protocol, electronic data entry forms may be completed online by study staff.

Data will be housed in the Memorial Sloan Kettering Cancer Center's (MSKCC) New Jersey data center. REDCap has been approved by MSKCC's Information Security to store PHI. The MSKCC Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections to ensure data is protected. The server is backed up nightly in the event that disaster recovery would be necessary and system would need to be rolled back. Members of the Clinical Research Administration supporting the REDCap software will have access to REDCap projects for the purpose to ensuring the proper functioning of the database and the overall software system.

Permissions to the database for internal will be managed by the REDCap project manager or study staff. User access to the data is contingent on those a part of the study team and data sharing agreements in place with third party entities if applicable. Project managers are responsible for regularly auditing these permissions to ensure changes in staff are reflected appropriately.

REDCap has the ability maintain an audit trail of changes to the database providing a timestamp as well as the user making the update. In addition, a data resolution module offers the ability of opening and closing queries optionally requiring justification when data is being updated. Permission roles for data resolution are integrated in REDCap. Comprehensive system logs are also maintained of user activity and when changes to the database are made.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

Additionally, a photograph of the patient's wrist will be captured by the researchers with an MSK-managed device to demonstrate that the electrodes placement on the participant's wrist is properly aligned. Participants will not be identifiable in the photographs and the photograph will not include any protected health information (PHI). The photograph will be shared with GE Healthcare, the device manufacturer, for validation that the electrodes are placed correctly. Data will be reported to the IRB as required. We estimate accrual to be approximately 2-3 patients per week allowing completion and reporting of the study within 1-2 years.

DATA TO BE COLLECTED

- Name
- MRN
- Date of birth
- Date of operation
- Sex
- ASA status
- Race
- Height
- Weight
- BMI
- Comorbidities
- Preoperative Medications/Intraoperative Medications/Postoperative Medications
- Rocuronium infusion rate
- Sugammadex dose
- IAP recorded every 15 minutes & additional time points, if applicable
- Surgical Assessment (Leiden scale) recorded every 30 minutes
- Volume and types of fluids intraop, including blood products
- Estimated blood loss
- Surgery start and end times
- Stage of disease
- Grade 3 or greater complications as described according to the MSKCC Graded Postoperative Complications Criteria
- Cause of death (if known)
- LOS
- Postoperative pain (surgical and shoulder) and nausea at postoperative time points
- Surgeon assessment of arm to which their patient was assigned
- RASS scores
- All requests by surgeons to vary IAP (independent of actual change in IAP)
- Gabapentin Pre-Operative and Post-Operative dose
- Position of electrode on wrist (collected by an MSK managed device in the OR)
- NPS scores

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year, more frequently if indicated.

The principal investigator will maintain final responsibility for the maintenance, quality and integrity of all data collection during the study and during the final analysis of data. Breaches of protocol, problems with eligibility, informed consent or discrepancies in data accuracy will be reported to the IRB at MSKCC as required.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the Document entitled ”Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials,” which can be found at: http://cancer.gov/clinicaltrials/conducting/dsm-guidelines. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC Data and Safety Monitoring Plans.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control. In addition, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

- The responsible PI will ensure that this study is conducted in agreement with the declaration of Helsinki (Tokyo, Venice, Hong King, Somerset West and Edinburgh amendments). The study will seek to protect the rights of human subjects in every way.
- The potential risks, including adverse drug reactions and potential benefits in terms of postoperative recovery will be discussed in detail with the patients.
- Potential side effects will also be discussed with the patients.
- No patient will be required to participate in the study and participation, or refusal to do so, will not affect the patient’s care or treatment.
- The patient will not incur any financial cost as a result of participation in the study.
- Participation will be purely voluntary, and subjects will not be reimbursed for participation in the study.

- Throughout the study, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular patient in the study.

All adverse events will be fully disclosed to the IRB in a timely fashion as required.

17.1 Privacy

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected

- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1

There is no additional SAE reporting information required by the funding source.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

- Appendix 1: Intraoperative Data Collection Sheet
- Appendix 2: Postoperative Data Collection Sheet
- Appendix 3: Scripted assessment of surgical conditions
- Appendix 4: Rocuronium infusion rates
- Appendix 5: Dosing for reversal of neuromuscular blockade
- Appendix 6: Scripted response for request to change IAP or verify IAP level intraoperatively
- Appendix 7: RASS Scores (Richmond Agitaiton and Sedation Scale)
- Appendix 8: GE Healthcare quick guide for NMT monitoring
- Appendix 9: Sugammadex FDA Label