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A prospective, randomized, single-blinded, non-inferiority study to evaluate the safety and efficacy of the saline-coupled bipolar sealer compared to the unipolar electrocautery in primary unilateral total knee arthroplasty

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|---|---|
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## Table of Contents

## List of Abbreviations

| | |
|---|---|
| **ASA** | American Society of Anesthesiologists |
| **AST** | Association of Surgical Technologists |
| **BMI** | Body Mass Index |
| **BID** | 2 times a day |
| **CC** | Cubic Centimeters |
| **CDRH** | Center for Devices and Radiological Health |
| **DVT** | Deep Vein Thrombosis |
| **IV** | Intravenous |
| **KG** | Kilograms |
| **KSS** | Knee Society Score |
| **MG** | Milligrams |
| **NS** | Normal Saline |
| **OR** | Operating Room |
| **PACU** | Post Anesthetic Care Unit |
| **PE** | Pulmonary Embolus |
| **PO** | By Mouth |
| **PST** | Pre-surgical Testing |
| **RCT** | Randomized controlled trial |
| **RF** | Radiofrequency |
| **THA** | Total Hip Arthroplasty |
| **TKA** | Total Knee Arthroplasty |
| **TXA** | Tranexamic acid |

## Study Summary

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|---|---|
| Title | A prospective, randomized, single-blinded, non-inferiority study to evaluate the safety and efficacy of the saline-coupled bipolar sealer compared to the unipolar electrocautery in primary unilateral total knee arthroplasty |
| Short Title | Saline-coupled bipolar sealer compared to the unipolar electrocautery in primary unilateral total knee arthroplasty |
| Protocol Number | |
| Phase | |
| Methodology | Prospective, Randomized, Single-Blinded, Non-inferiority Study |
| Study Duration | 2 years |
| Study Center(s) | Single-center /Syosset Hospital |
| Objectives | *Primary Objective*<br>• To assess whether the unipolar electrocautery is non-inferior to saline-coupled bipolar sealer with respect to estimated blood loss as calculated by Gross' formula in patients undergoing primary unilateral total knee arthroplasty.<br>*Secondary Objective*<br>• To assess whether the unipolar electrocautery is superior to saline-coupled bipolar sealer with respect to hemostasis in patients undergoing primary unilateral total knee arthroplasty.<br>• To assess whether hospital length of stay in patients undergoing primary unilateral total knee arthroplasty is different between the saline-coupled bipolar sealer compared to the unipolar electrocautery.<br>• To assess whether objective and functional outcomes in patients undergoing primary unilateral total knee arthroplasty differ between the saline-coupled bipolar sealer compared to the unipolar electrocautery.<br>• To assess the safety profile of the saline-coupled bipolar sealer compared to the unipolar electrocautery in patients undergoing primary unilateral total knee arthroplasty |
| Number of Subjects | 164 |
| Diagnosis and Main Inclusion Criteria | Primary Unilateral Total Knee Arthroplasty (TKA) |
| Study Product, Dose, Route, Regimen | Aquamantys System™ Medtronics Saline-Coupled Biopolar Sealer |
| Duration of administration | Intraoperative |
| Reference therapy | Covidien ForceTriad™ Electrosurgical System<br>Unipolar Electrocautery System |

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| Statistical Methodology | The test for non-inferiority will be carried out using a 2-tailed 95% confidence interval for the difference (δ = Unipolar electrocautery system - Saline-coupled bipolar sealer) in the estimated blood loss between the two groups. δ is the margin of inferiority and will be set at 200 cc. If the upper confidence limit < δ (≥δ) then we will conclude that the Unipolar electrocautery system is non-inferior (inferior) to the Saline-coupled bipolar sealer.<br><br>This test for non-inferiority will only be performed for the primary study endpoint of estimated blood loss; all other secondary variables will be tests of superiority of Unipolar electrocautery versus Saline-coupled bipolar sealer. |

## 1 Previous Study History

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

☒ No ☐ Yes – if yes, please explain:

## 2 Brief Summary of Research

Total joint arthroplasty can result in significant blood loss. Minimizing blood loss has led to multiple blood conservation strategies in orthopaedic procedures. The use of unipolar electrocautery or the saline-coupled bipolar sealer are methods used to reduce intraoperative bleeding.

Saline-coupled bipolar sealer technology initially demonstrated promising results in the literature when it was reported that this technology had superior efficacy by reducing blood loss and transfusion requirements in orthopaedic surgery. However, the saline-coupled bipolar sealer technology comes at a significantly higher cost when compared to the unipolar electrocautery. A bipolar electrode costs an additional $450.00 per case, whereas, the unipolar electrocautery catheter is included in all the pre-packaged orthopedic surgical trays. The added cost of the saline-coupled bipolar sealer was offset by the potential savings in the reduced need for blood transfusions. A single blood transfusion is estimated to be $750-$1200. [1] This cost includes both the direct cost of the blood and the additional nursing time needed. Recent publications have challenged the superiority of the saline-coupled bipolar sealer in hemostasis. These randomized clinical trials (RCT) have not supported superiority of this method when compared to standard unipolar electrocautery and the continued use of the saline-coupled bipolar sealer has been questioned.

The purpose of this study is to investigate whether the saline-coupled bipolar sealer compared to the unipolar electrocautery provides superior hemostasis in patients undergoing primary unilateral total knee arthroplasty. This will be a prospective, randomized, single-blinded, non-inferiority study in patients scheduled for a primary unilateral TKA with Dr. Eugene Krauss or Dr. Ayal Segal. The restriction of this study to two surgeons will limit variations in the outcomes being measured due to differences in surgical technique.

# 3 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

## *3.1 Background*

Total joint arthroplasty can result in significant blood loss. Transfusion rates have been reported to be as high as 39% in total knee arthroplasty.[2] Transfused patients are exposed to risks such as adverse immunological reactions, disease transmission, intravascular hemolysis, transfusion-induced coagulopathy, renal impairment or failure, and increased mortality. Postoperative anemia has also been associated with prolonged length of stay and increased hospital costs[3]. Minimizing blood loss has led to multiple blood conservation strategies in orthopaedic procedures.

One method of hemostasis in use at Syosset Hospital since March 2013 is the use of intravenous antifibrinolytics (tranexamic acid). The use of tranexamic acid (TXA) in orthopaedic surgery has resulted in a 50% reduction in the rate of transfusions[4]. TXA interferes with clot breakdown. Ninety percent of TXA is excreted by the kidneys after approximately 24 hours. However, there have been isolated case reports of thrombus formation with intravenous (IV) administration of TXA. Due to this risk, IV TXA is not administered to patients with risk factors for thromboembolic events.

Epidural or spinal anesthesia (neuraxil blockade) has been shown to be effective in reducing intraoperative blood loss. Rogers, et al in a meta-analysis of 473 patient in 16 trials reported the requirement for a transfusion of two or more units of blood was reduced by about half in patients allocate to neuraxial blockade.[5] Spinal or Epidural anesthesia causes a sympathetic nerve block leading to vasodilatation distal to the site of anesthesia. This effect is responsible for the reduction in bleeding during surgery.

Maintenance of normothermia is also of paramount importance in controlling blood loss in orthopedic surgery. Perioperative hypothermia is defined as a core temperature $< 36^0$ C. Prospective trials have shown that the maintenance of normothermia is associated with reductions in blood loss, the requirements for allogeneic blood products, postoperative infections, and shorter hospital stays. [6]

Another method used intraoperatively to maintain hemostasis is the application of a pneumatic tourniquet. During TKA a pneumatic tourniquet is applied to the upper part of the thigh on the operative limb and inflated to a pressure determined by the surgeon. The pneumatic tourniquet is utilized during extremity surgery to maintain a bloodless field. The tourniquet applies pressure to the limb to occlude the blood supply. The tourniquet is released by the surgeon at the end of the case and electrocautery is then used to seal any bleeding vessels.

The insertion of a suction drain, once a common practice in orthopedic surgery, has become controversial. A closed suction drainage system is believed to increase bleeding because the tamponade effect of a closed and undrained wound is eliminated. Multiple publications have questioned the routine insertion of drains. Esler, et al prospectively randomized 100 patients undergoing cemented total knee replacement to receive either a single deep closed-suction drain or no drain. The total blood loss was significantly greater in those with a drain (568 ml versus 119 ml, $p < 0.01$; 95% CI 360 to 520) although those without a drain lost more blood into the dressings (55 ml versus 119 ml, $p < 0.01$; 95% CI –70 to10). There was no statistical difference in the postoperative swelling or pain scores, or in the incidence of pyrexia, ecchymosis, time at which flexion was regained or the need for manipulation, or in the incidence of infection at a minimum of five years after surgery in the two groups. The authors concluded that there was no evidence to support the use of a closed-suction drain in cemented knee arthroplasty, finding it merely interfered with mobilization and complicated nursing care. [7]

Electrocautery has emerged as an imperative adjunct to surgery across the entire range of surgical disciplines. In 1926 William T Bovie, a physicist, developed the electrocautrery. Harvey Cushing introduced it into clinical practice. A diathermy machine converts electricity of the main supply (240V; 50 Hz) into high frequency current (>100,000 Hz) to minimize the risk of electrical shocks. In unipolar mode, the current from the diathermy enters the patient through the active electrode and exits through the grounding pad. The unipolar electrocautery results in a tissue surface above $400^0$ C to char tissue.

In saline-coupled bipolar mode the current passes between the two prongs of the electrode without any significant flow through the patient and there is no need for the grounding pad. The use of saline-coupled bipolar sealing technology (Aquamantys System®, Medtronic) represents a newer approach to reducing blood loss in patients undergoing total joint arthroplasty. Unlike standard electrocautery, which uses unipolar radiofrequency energy, this technology uses bipolar radiofrequency energy combined with a continuous-flow saline at the electrode tip to prevent tissue temperatures from exceeding 100°C. The temperature is sufficient to shrink collagen fibers in blood vessel walls, which seals their lumen resulting in hemostasis without surrounding tissue damage[2]. Saline-cooled bipolar radiofrequency technology provides a solution to osseous bleeding by using saline as a conduit into the interstices of cancellous bone.[8] Another advantage of this technology over standard electrocautery is the ability to not only spot coagulate vessels but also broadly paint surfaces that could ooze after the soft tissues have been closed.[2] However, the use of this technology has significantly increased the per-case expense of using this device.

The use of the saline-coupled bipolar sealer in orthopedics has become more prevalent based on initial publications showing a reduction in intraoperative blood loss and postoperative transfusion requirements. Marulanda, et al conducted a randomized controlled trial (RCT) in 2009 with 69 primary TKA patients. Though the bipolar sealer group had a lower mean decline in hemoglobin level compared to the unipolar group, there was not a statistically significant difference in blood transfusions or postoperative hemoglobin nadir.[2] Clinical outcomes were assessed by length of stay, range of motion and Knee Society Scores. There were no differences in clinical outcomes between the groups.

In 2009 Weeden, et al published a retrospective, matched controlled review of 100 patients who had undergone primary total knee arthroplasty by a single surgeon. The prevalence of both autologous and allogeneic transfusion was significantly reduced by 64% in the bipolar sealing group.[9] However, this study did not measure any functional or safety outcomes. Additionally the authors did not describe their blood transfusion protocols.

Recent publications have challenged the efficacy of the saline-coupled bipolar sealer method of hemostasis. Recently published randomized clinical trials have not supported superiority of this method when compare to standard unipolar electrocautery. Plymale, et al in 2012 conducted a RCT in 113 patients undergoing primary TKA. The patients were randomized to either unipolar electrocauterization or the bipolar sealer. Plymale reported no significant difference in postoperative drain output, postoperative hemoglobin and hematocrit values or transfusion requirements.[2] The study included 3 surgeons. The patients underwent general or epidural anesthesia. To minimize variability in surgical technique the study developed a strict intraoperative coagulation protocol. All patients in this study had an autotransfusion drain inserted and all patients received autodrain transfusions within the first 4 hours postoperatively. Blood transfusions were left to the discretion of each surgeon as there were no standard blood transfusion protocols in place at the investigative site.

Mixed results have also been found in the use of the saline-coupled bipolar sealer in total hip arthroplasty (THA). Morris in a retrospective study supported previous authors' findings of significant reductions in blood loss and transfusions with the use of the saline coupled bipolar sealer in THA. [10] However, in a prospective randomized clinical trial Morris found that there was no clinically significant difference in the actual blood loss, hemoglobin levels, or transfusion rates. [11] Zeh, et al also found no clinically relevant advantage for the use of the bipolar sealer in comparison to the unipolar sealer for blood management in primary THA. [12] Due to the higher cost both authors do not recommend the use of the bipolar sealer for primary THA.

These conflicting results are multifactorial and highlight both the rapidly changing landscape of orthopedic surgery and faults in study design. The restriction of this study to two surgeons will limit variations in the outcomes being measured due to differences in surgical technique.

Plymale's study included patients having either general or epidural anesthesia. Baseline characteristics did not discuss if these groups were evenly distributed.

These studies predate the use of IV TXA in orthopedic surgery and its dramatic effect on hemostasis. Additionally, current trends in allogeneic blood transfusion protocols have also changed. Patients are now transfused at lower hemoglobin levels. Some of these studies did not have a clearly defined transfusion protocol and the transfusion requirements were left to surgeon discretion. This limitation allowed for operator bias of a study clinical outcome.

Another concern for using drain output as an outcome measure is that it has been documented that this drainage does not accurately represent postoperative blood loss as the drains do not remove all the blood lost.[13] In a study by Johansson and colleagues drain output was shown to be inaccurate as a measure of postoperative blood loss as the drain does not account for hidden blood loss. [14]

Efficacy and safety data are lacking in these publications as most patients are observed in the hospital setting only. Long term follow-up on clinical outcomes such as range of motion and functional assessment scores were not reported in many of the trials.

This study will compare the use of the saline-coupled bipolar sealer with the unipolar electrocautery to determine if one method results in increased homeostasis as measured by a hemoglobin nadir, reduced allogeneic blood transfusions, and estimated blood loss calculated using the Gross' Formula. This study will also be assessing the length of hospital stay, 2012 Knee Society Scores, and the safety profile.

Null Hypothesis: Our hypothesis is that the difference between the mean estimated blood loss in the Unipolar electrocautery and the saline-coupled bipolar sealer is greater than or equal to the margin of non-inferiority of 200 cc. Also, we propose that the safety and efficacy profile of the saline-coupled bipolar vs. the unipolar are clinically equivocal.

### *3.2 Investigational Agent-Device*

The Aquamantys® System is a commercially available device used routinely used in the operating room for a wide variety of surgical cases. The Aquamantys® System is a patented Transcollation® technology, a combination of radiofrequency (RF) energy and saline that provides haemostatic sealing of soft tissue and bone during surgery. The patented integration of RF energy and saline delivers controlled thermal energy to tissue. This combination allows the device temperature to stay at approximately 100°C, nearly 200°C less than conventional devices, which produces a tissue effect without the charring associated with other methods. The temperature is sufficient to shrink collagen fibers in the walls of blood vessels, effectively sealing the blood vessels, resulting in the reduction in bleeding from both soft tissue and bone. The device can be used to spot coagulate vessels that are actively bleeding or to broadly paint tissue surfaces to prevent bleeding or treat active oozing. Suction is used to remove the saline from the surgical field.

The Aquamantys System consists of a generator and disposable, single-use hand pieces. Medtronic Advanced Energy offers innovative Aquamantys hand pieces that are adept for use in orthopaedic surgery, such as the 6.0 Bipolar Sealer and MBS Bipolar Sealer with Light. Salient Surgical Technologies, the original manufacturer of the device was acquired by Medtronic in 2011.

Aquamantys Disposable Bipolar Devices are sterile, single-use devices which employ RF energy and saline irrigation for hemostatic sealing and coagulation. These devices are equipped with a dual electrode tip. Saline and electrical lines exit the opposite end of the hand piece from the dual electrode. The hand piece is equipped with an on/off button that simultaneously activates both RF power and saline flow. A saline fluid delivery line is provided with the device, and includes a section of pump tubing and drip chamber. The three-pin electrical connector is designed to be plugged into the Aquamantys Pump Generator (Appendix A).

The Coviden ForceTriad™ energy platform is a full-featured electrosurgical system that provides electrosurgical cutting and coagulation, bipolar functionality, and vessel sealing in a single generator (Appendix B).

Dr. Krauss has been a practicing orthopaedic surgeon since 1987. Dr. Segal has been a practicing orthopaedic surgeon since 2002. Both have extensive experience in the use of both the saline-coupled bipolar sealer and the unipolar electrocautery. They are experts in the use of these devices and have not had any reportable device related adverse events. Dr. Barry G.Simonson has been a practicing orthopaedic surgery for over 20 years and has extensive experience using both the saline-coupled bipolar sealer and the unipolar electrocautery.

The unipolar electrocautery has been in use throughout Northwell Health for over 50 years. The saline-coupled bipolar sealer has been use for about 5-6 years at multiple Northwell Health sites. Both systems have a proven safety profile for use in clinical practice.

The operating room staff is specially trained in the proper use of the saline-coupled bipolar sealer and the unipolar electrocautery. The operating room adheres to the Association of Surgical Technologists (AST) Standards of Practice for Use of Electrosurgery (Appendix C) and the Northwell Electrosurgical Safety Policy (Appendix D). The AST developed these standards of practice to protect both the patient and hospital staff. These practices provide an optimum level of patient safety.

### *3.3 Preclinical Data*

This section is not applicable to this study. These devices are commercially available.

### *3.4 Clinical Data to Date*

This section is not applicable to this study. These devices are commercially available.

### *3.5 Dose Rationale and Risk/Benefits*

This section is not applicable to this study.

## 4 Study Objectives

*Primary Objective*

- To assess whether the unipolar electrocautery is non-inferior to saline-coupled bipolar sealer with respect to estimated blood loss as calculated by Gross' formula in patients undergoing primary unilateral total knee arthroplasty.

*Secondary Objective*

- To assess whether the unipolar electrocautery is superior to saline-coupled bipolar sealer with respect to hemostasis in patients undergoing primary unilateral total knee arthroplasty.

- To assess whether hospital length of stay in patients undergoing primary unilateral total knee arthroplasty is different between the saline-coupled bipolar sealer compared to the unipolar electrocautery.

- To assess whether objective and functional outcomes in patients undergoing primary unilateral total knee arthroplasty differ between the saline-coupled bipolar sealer compared to the unipolar electrocautery.

- To assess the safety profile of the saline-coupled bipolar sealer compared to the unipolar electrocautery in patients undergoing primary unilateral total knee arthroplasty

# 5 Resources Available to Conduct the Human Research

For the calendar years 2013 to 2015 Dr. Krauss performed 950 primary total knee arthroplasties and Dr. Segal performed 326 primary total knee arthroplasties.

Prior to conducting any study related procedures the Principal Investigator or a designee will train all applicable hospital staff on the protocol and study related activities to ensure study compliance.

# 6 Study Design

## *6.1 General Design*

This is a prospective, single center, randomized, single-blinded, non-inferiority study to evaluate the safety and efficacy of the bipolar sealer compared to the unipolar in primary, unilateral total knee arthroplasty. The restriction of this study to three surgeons will limit variations in the outcomes being measured due to differences in surgical technique.

Current preoperative, intraoperative, and postoperative blood management strategies will be consistent for all subjects.

Patients seen in the outpatient office and scheduled for primary unilateral TKA by Dr. Krauss, Dr. Segal, or Dr. Barry Simonson will be approached for inclusion in the clinical trial. Dr. Krauss, Dr. Segal, Dr. Simonson, or their designee, will discuss the study with the patient. The

patient will be given sufficient time to read the consent and ask any questions. The informed consent will be obtained by Dr. Krauss, Dr. Segal or Dr. Simonson.. No study related procedures will be done prior to obtaining the informed consent.

Objective and functional outcomes will be obtained using the 2011 Knee Society Score (KSS). The KSS will be completed preoperatively and postoperatively as per the department standard of care for all total knee arthroplasty patients.(Appendix E).
Preoperatively patients taking anticoagulants or antiplatelets, with the exception of aspirin 81 mg qd, will be excluded from the study as these medications could adversely affect intraoperative and postoperative bleeding. Patients with any bleeding dyscrasias will also be excluded from the study. Patients are instructed to discontinue aspirin, medications containing aspirin-like products, and non-steroidal anti-inflammatory agents seven days prior to surgery. (Appendix F). Patients who are unable to stop these products for any reason will be excluded from the study.

All preoperative patients are seen in pre-surgical testing (PST) within 4 weeks prior to the scheduled surgery. Laboratory testing done as standard of care for all preoperative surgical patients are comprehensive metabolic panels and complete blood count. These laboratory values will be used to evaluate the inclusion and exclusion criteria for study enrollment. This study does not require any study specific laboratory tests. Patients are counseled by the nurse practitioner in PST on prescription medications, over-the-counter medications, foods, herbs and supplements that will interfere with blood clotting and must be discontinued prior to surgery (Appendix G).

On the operative day patients will be interviewed to confirm their agreement to continue in the study. Patients will be re-consented by Dr. Krauss, Dr. Segal, or Dr. Simonson, if the date of the original consent is greater than 28 days from the date of surgery. The inclusion and exclusion criteria will be verified prior to study randomization using the laboratory testing done in PST and the preoperative medical history documents. Patients will be randomized to either the treatment arm (saline-coupled bipolar sealer) or the control arm (unipolar electrocautery). The Biostatistics Unit will develop a randomization procedure using a permuted block design and the randomization process will occur in REDCap using the Randomization Module. The operating room (OR) staff will be immediately notified of the treatment arm so that the OR can be prepared.

Intraoperative blood management strategies will be consistent for all subjects to avoid any confounding factors which could affect postoperative transfusion requirements. Any patients unable to be treated according to the department treatment guidelines will be excluded from the study. Intraoperatively blood loss is minimized by anesthetic techniques, pharmacologic interventions, and surgical techniques.

Anesthetic techniques include spinal anesthesia. Spinal anesthesia is the preferred method of anesthesia for patients having a TKA. Any patient with preoperative contraindications to spinal anesthesia will be excluded from the study. Unfortunately, due to technical issues in the OR, some patients are unable to receive spinal anesthesia and the patient is given general anesthesia. Though a rare occurrence these patients will remain on study and included in the study statistics as this is an Intent to Treat Study design. Euthermia is managed by the anesthesiologist with the use of warming blankets.

Pharmacologic techniques included TXA 1000 mg/100cc Normal Saline infused over 15-30 minutes x 2 doses. The first dose will be given prior to incision and the second dose will be given when the pneumatic tourniquet is released or at least 60 minutes after the first dose. Any patients unable to be treated according to the department treatment guidelines for IV TXA will be excluded from the study (Appendix H). A closed suction drain is inserted based on the surgeon's clinical decision.

The patient and the postoperative hospital staff will be blinded to the treatment arm. The OR staff will be trained not to discuss this information with the patient. During the transition of care from the OR to the Post Anesthetic Care Unit (PACU) the electrocautery used is not routinely included in the verbal patient report. The lack of this information is not required to effectively manage the patient in the postoperative period and will not affect patient care. Postoperatively medical care is managed by the hospitalist, medical doctors specializing in the care of hospitalized patients. The blood transfusion protocol is consistent for all patients. Patients receive allogeneic blood transfusions when the hemoglobin is $\leq$ 7 g/dL. For Hgb >7 g/dL to <8 g/dL patients are treated only if they are exhibiting clinical symptoms related to the anemia or if there is a rapid decline in Hgb. For Hgb $\geq$ 8 g/dL patients are treated if they are exhibiting clinical symptoms of anemia.

The pneumatic tourniquet will be applied and inflated to maintain a bloodless field. The tourniquet pressure is determined by the surgeon. At the end of the surgery the tourniquet is released. Bleeding vessels are sealed with either the saline coupled bipolar sealer or the unipolar electrocautery based on the subject randomization.

Venous thromboembolism prophylaxis in joint replacement consists of both chemical and mechanical measures. All patients have a sequential compression device applied in the operating room to the non-operative extremity. At the end of the surgical case, after the dressing has been applied, the sequential compression device is applied to the operative extremity. Sequential compression devices are in use while patients are in bed.

Patients are started on venous thromboembolism prophylaxis postoperative Day 1. The treatment regimen is dependent on the patient's calculated Caprini Risk Assessment Score. (Appendix I).

Early ambulation for TKA patients begins on postoperative Day 0. Patients are seen by a physical therapist within four hours of discharge from the PACU to begin their ambulation. Only acute medical events are valid reasons for a patient not to be ambulated at this time point. While hospitalized patients are visited daily by a physical therapist. This study will be assessing the physical therapy progress of the patients by collecting the total distance walked each day. The physical therapists will be blinded to the treatment arm of the study.

Estimated blood loss will be calculated using the Gross' Formula.[16] This method is being used to provide a more standardized method of calculating blood loss. Eipe and Ponniah showed that surgical blood loss was underestimated by 64% when clinical methods are used to assess blood-soaked sponges and blood lost to suction bottles and the vacuum drain[17].

Following discharge patients will be followed in the outpatient office according to the postoperative standard of care visit schedule. The 2011 KSS Objective Outcome Measurements will be collected at the postoperative 2 week and 8 week visits, or the office visit closest to these time points. The 2011 KSS Functional Outcome Measurements will be collected at the 8 week visit or the postoperative office visit closest to this time point. Patients will be followed for 90 days from the date of surgery for any device related adverse events and surgical site infection.

### *6.2 Primary Study Endpoints*

**Primary Study Endpoints:**

- Perioperative estimated blood loss as calculated by the Gross' Formula

**Secondary Study Endpoints**:

- Need for allogeneic red blood cell transfusions
- Perioperative blood loss as measured by the difference between the:
    - preoperative hemoglobin and the nadir of the postoperative hemoglobin value during the hospital stay
    - the preoperative hematocrit and the nadir of the postoperative hematocrit value during the hospital stay
- Hemoglobin and hematocrit values over time (pre-op, post-op day 0, day 1, day 2, and until discharge)
- Hospital LOS
- Functional outcomes as measured by:
    - distance walked in feet
    - 2011 Knee Society Scores

**Primary Safety Endpoints**:

- Wound infections within 90 days of the date of surgery
- Device related adverse events within 90 days of the date of surgery

## 7 Subject Selection and Withdrawal

### *7.1 Inclusion Criteria*

1. Patients scheduled for primary unilateral total knee arthroplasty
2. Preoperative Hemoglobin >11mg/dL
3. Preoperative platelet count of >150,000
4. Age ≥18
5. Patient is freely able to provide consent

6. American Society of Anesthesiologists (ASA) classification I-III (Appendix J)
7. Patient willing to complete all study related procedures

### *7.2 Exclusion Criteria*

1. Patients allergic to aspirin
2. Patients unable to take to aspirin for VTE prophylaxis for any reason
3. Patients with a contraindication to Apixaban
4. Any patient who is not a candidate for VTE risk stratification according to the calculated Caprini Risk Assessment Score (Appendix I). This includes, but is not limited to, any patient who cannot be prescribed ASA 81 mg bid or Apixiban 2.5 mg bid for VTE prophylaxis
5. Patients who for any reason are not a candidate for the use of the monopolar electrocautery
6. History of venous thromboembolism (Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE)) within 12 months prior to the date of surgery
7. Mitral valve replacement or aortic valve replacement with additional risk factor for stroke (atrial fibrillation, previous thromboembolism, left ventricular dysfunction, hypercoagulable conditions)
8. Active cancer
9. Inheritied thrombophilia, eg: Factor V Leiden, Protein C and S deficiencies, Antithrombin deficiency, Prothrombin 20210A mutations
10. Acquired thrombophilia, eg: Lupus anticoagulant, antiphospholipid antibody syndrome
11. Patients taking clopidogrel (Plavix), ticagrelor(Brilinta), or prasugrel (Effient) or any other antiplatelet medication (except for aspirin 81 mg)
12. Patients unable to get IV TXA for any reason
13. Patients requiring anticoagulant treatment prior to surgery
14. History of stroke or TIA
15. Serum creatinine > 2.8 mg/dl
16. History of hepatic failure

17. Any medical condition that in the opinion of the investigator would require special fluid management protocols during or after surgery
18. Allergy to TXA
19. Preoperative hemoglobin $\leq$ 11
20. Preoperative platelets $\leq$ 150,000
21. Blood transfusion within 1 month of surgery
22. ASA classification IV or V
23. Patients who are unwilling to undergo blood transfusion, if necessary
24. Evidence of active (systemic or local) infection at time of surgery
25. Patients who have habitual opioid use
26. Patients who have a psychiatric or mental illness which could impair the consent process or ability to complete patient-reported questionnaires
27. Fixed motor deficit affecting functional assessment of the knee
28. Patients unable to have spinal anesthesia
29. Patients receiving erythropoietin therapy for anemia
30. Patients who are unable to stop their daily aspirin, aspirin-like products, and/or non-steroidal anti-inflammatory agents 7 days prior to surgery for any reason
31. Patients with a contraindication for the pneumatic tourniquet applied in the operating room

### *7.3 Vulnerable Populations*

No vulnerable patients will be enrolled in this clinical trial. Only patients who are scheduled for elective total knee arthroplasty will be approached for enrollment.

### *7.4 Subject Recruitment and Screening*

Patients scheduled for primary unilateral total knee replacement surgery by Dr. Krauss or Dr. Segal will be approached for inclusion in the clinical trial.

### *7.5 Consent Process*

Participation in the clinical trial will be discussed with the patient by the Dr. Krauss, Dr. Segal, Dr. Simonson or their designee, when the patient is first scheduled for a total knee arthroplasty. The investigator will discuss the following:

- the purpose/objective of the study
- the study design (e.g., the number of participants)
- how patients are assigned to the treatment group
- participation in this study is not required
- patients may withdraw from this study at their discretion

Patients will be given ample time to review the consent and ask questions. Those wishing to participate will sign the informed consent form. The consent process will be documented by the investigator on the study "Enrollment Note". A copy of the signed consent will be provided to the patient. Patients without capacity to provide informed consent will be excluded from the study.

Patients will be reconsented if the consent process was done >28 days prior to surgery.

### *7.6 Early Withdrawal of Subjects*

#### 7.6.1 When and How to Withdraw Subjects

Patients may withdraw from the study at any time without bias.

#### 7.6.2 Data Collection and Follow-up for Withdrawn Subjects

Any paper documents that contain PHI (e.g., link between the ID to subjects' identifiers) will be stored in a locked cabinet within the research department, separately from any de-identified research documents. IRB-approved personnel will be the only individuals with access to any research documents containing PHI. Any electronic documents that contain PHI will be stored on REDCap. The Feinstein Institute for Medical Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Biostatistics Unit of the Feinstein Institute for Medical Research. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at the Feinstein and all web-based information transmission is encrypted. REDCap was developed specifically

around HIPAA-Security guidelines and is recommended to Northwell Health researchers by our Clinical Research Service, Research Compliance Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports 1,244 active institutional partners and other institutions in 87 countries (www.project-redcap.org). No PHI or research data will be stored on any Portable Electronic Devices (e.g., laptops, tablets, flash drives, etc.). Any research data that will be emailed will be de-identified and encrypted. PHI will not be emailed to any commercial email addresses (e.g., Gmail, Yahoo, Hotmail).

Additional information collected will include:

1. Initals
2. Medical record number
3. Date of surgery
4. Race/Ethnicity
5. Significant past medical and surgical history
6. Age
7. Height (cm)
8. Weight (kg)
9. Body mass index ($kg/m^2$)
10. Calculated Caprini Score
11. Preoperative 2011 Knee Society Score Objective and Functional Assessments
12. ASA classification
13. Length of procedure in minutes (from first incision to incision closure)
14. Pneumatic Tourniquet time (in minutes)
15. Type of anesthesia (spinal/general)
16. Closed Suction Drain inserted (Yes/No)
17. Date drain discontinued (if applicable)
18. Total amount of drainage in cc
19. Temperature on arrival to the PACU
20. Length of time in minutes to reach normothermia in the PACU ($T \geq 36^0$ C)
21. Patient out of bed within 4 hours of discharge from the PACU (Yes/No)
22. Baseline Hemoglobin

23. Baseline Hematocrit
24. Baseline Platelets
25. Postoperative Day 0 until discharge:
    - Number transfusions
    - Daily Hemoglobin (standard of care for postoperative patients)
    - Daily Hematocrit (standard of care for postoperative patients)
    - Daily Platelets (standard of care for postoperative patients)
    - Ambulation (in feet)
    - Assessment for device related adverse events
    - Assessment for wound infection
26. Discharge disposition
27. Discharge Date
28. Postoperative 2011 Knee Society Score Objective Outcome Measurements will be collected at the 2 week and 8 week visits, or the postoperative visit closest to these time-points
29. The Postopertative 2011 Knee Society Score Functional Outcome Measurements will be collected at the 8 week visit or the postoperative visit closest to this time-point.
30. Assessment for wound infection for 90 days from the date of surgery
31. Assessment for device related adverse events for 90 days from the date of surgery

# 8 Study Drug/Device

## *8.1 Description*

See Appendix A & B for details on the commercially available devices being used.

## *8.2 Treatment Regimen*

This section is not applicable for this study.

### *8.3 Method for Assigning Subjects to Treatment Groups*

Subjects will be randomly assigned by a 1:1 ratio to either:

1. **Unipolar electrocautery system** (Covidien ForceTriad™ Electrosurgical System)
2. **Saline-coupled bipolar sealer** (Aquamantys System™ Medtronics)

The Biostatistics Unit will develop a randomization procedure using a permuted block design and the randomization process will occur in REDCap using the Randomization Module. Details, including required record keeping and a well documented single-blind randomization procedure, will be further developed upon approval of this protocol.

### *8.4 Preparation and Administration of Study Drug/Implantation of Study Device*

This section is not applicable for this study.

### *8.5 Subject Compliance Monitoring*

This section is not applicable for this study.

### *8.6 Prior and Concomitant Therapy*

Patients taking clopidogrel (Plavix), ticagrelor(Brilinta), prasugrel (Effient) or warfarin (Coumadin) preoperatively will be excluded from enrollment.

### *8.7 Packaging*

This section is not applicable for this study.

### *8.8 Blinding of Study Drug/Device*

Blinding of the principal investigator and operating staff is not possible. However, all attempts will be made to keep this information from the hospital staff caring for the patients in the postoperative period. The patient and the postoperative hospital staff will be blinded to the treatment arm. The OR staff will be trained not to discuss this information with the patient. During the transition of care from the OR to the Post Anesthetic Care Unit (PACU) the treatment arm will not be included in the verbal patient report. The lack of this information is not required to effectively manage the patient in the postoperative period and will not affect patient care.

Postoperatively medical care is managed by the hospitalist, medical doctors specializing in the care of hospitalized patients.

### *8.9 Receiving, Storage, Dispensing and Return*

#### 8.9.1 Receipt of Drug Supplies/Device

The saline-coupled bipolar sealer and the unipolar electrocautery are both commercially available products routinely used in the OR.

#### 8.9.2 Storage

This section is not applicable for this study.

#### 8.9.3 Dispensing of Study Drug/Device

This section is not applicable for this study.

#### 8.9.4 Return or Destruction of Study Drug/Device

This section is not applicable for this study.

## 9 Study Procedures

### *9.1 Visit 1-Preoperative office visit*

- Informed Consent
- Completion of the Preoperative 2011 Knee Society Score (done as part of the standard of care for all preoperative knee arthroplasty patients)

### *9.2 Visit 2-Day of Operation*

- Re-consent if applicable
- Verification of Inclusion/Exclusion Criteria
- Randomization and Notification of the OR staff

### *9.3 Visit 3-Hospital Postoperative Period: Postoperative Day 0 to Discharge*

- Device Adverse Event assessment
- Wound infection assessment
- Blood transfusions assessment
- Daily Hemoglobin, Hematocrit, and Platelets (standard of care for all postoperative surgical patients)
- Distance walked in feet as document by the Physical Therapy Department
- Suction drain output (if applicable)

### *9.4 Visit 4-Outpatient Postoperative Period (2 week and 8 week visit, or the visit closest to this time-point*

- Device Adverse Event Assessment
- Assessment for wound infection
- Completion of the Postoperative 2011 Knee Society Score

### *9.5 Visit 5-End of Study Visit (90 days or greater from the date of surgery)*

The patient will be contacted via phone 90 days or greater from the date of surgery to collect any adverse events related to the device and for any wound infections or blood transfusions+. All device related adverse events and wound infections will be followed until resolved. Patients enrolled in the study will be contacted using the orthopedic department's standard of care follow-up telephone call script (Appendix M). Three attempts will be made to contact the patient. Patients who are unable to be contacted after 3 attempts will be considered lost to follow-up.

## 10 Risks to Subjects

This study does not put the patient at any additional risk. The bipolar sealer and unipolar electrocautery are commercially available devices routinely used during orthopaedic surgery. Risk factors identified with the use of electrosugery include fires, patient burns, surgical personnel injuries and biological hazards, such as plume. The operating room adheres to the Association of Surgical Technologists (AST) Standards of Practice for Use of Electrosurgery (Appendix C) and the Northwell Health Electrosurgical Safety Policy (Appendix D). The AST developed these standards of practice to protect both the patient and hospital staff. These practices provide an optimum level of patient and operating room staff safety.

## 11 Potential Benefit to Subjects

Participating in this clinical study will contribute to current medical knowledge of these devices. The results of this study can make a difference in the care of future patients by providing information about the benefits of these interventions.

## 12 Research Related Harm/Injury

This study does not put the patient at any additional risk.

## 13 Provisions to Protect Privacy Interests of Subjects

Potential research patients will be identified in the private orthopaedic outpatient office. Enrollment in the trial will be discussed in a private room and the patient will be provided with ample time to review the consent and ask questions.

## 14 Statistical Plan

### *14.1 Sample Size Determination*

**Sample Size Considerations**:
The proposed sample size for this study is **164 subjects** (**n=82 per group**).

As a non-inferiority trial, Unipolar will be considered non-inferior to Bipolar if the difference in the mean estimated blood loss as calculated by Gross' Formula is less than 200 cc (δ=margin of inferiority=200 cc). More formally, let $\mu_{Unipolar}$ and $\mu_{Bipolar}$ be the mean estimated blood loss for the Unipolar system and the Bipolar system, respectively. The following are the null hypothesis and alternative hypothesis:

$H_0$: $d = \mu_{Unipolar} - \mu_{Bipolar} \geq \delta$ vs.
$H_A$: $d = \mu_{Unipolar} - \mu_{Bipolar} < \delta$

Based on a previous study "**To Evaluate the Safety and Efficacy of IA-TXA in Primary Total Joint Arthroplasty**" we will assume that the mean estimated blood loss is 1133 cc for both the unipolar and bipolar group. The common standard deviation of 511 cc was calculated based on the average estimated blood loss standard deviations in the Bipolar system and Unipolar system which were 476 cc and 546 cc, respectively (Marulanda, 2009). Based on two surgeons that are experts in TKA, less than 200 cc was determined to be a clinically acceptable increase in estimated blood loss. Using a 2-sided α-level of 0.05, and a non-inferiority margin of 200 cc, a target of 82 subjects per group (n=164 in total) would yield 80% power to determine that the Unipolar system is non-inferior to the Bipolar system when the estimated blood loss in the Bipolar group is 1133 cc and in the Unipolar group is 1133 cc with a common standard deviation of 511 cc.

***Statistical Methods***

**Primary Study Endpoints:**

- Perioperative estimated blood loss as calculated by the Gross' Formula

**Secondary Study Endpoints**:

- Need for allogeneic red blood cell transfusions
- Perioperative blood loss as measured by the difference between the:
    - preoperative hemoglobin and the nadir of the postoperative hemoglobin value during the hospital stay
    - the preoperative hematocrit and the nadir of the postoperative hematocrit value during the hospital stay
- Hemoglobin and hematocrit values over time (pre-op, post-op day 0, day 1, day 2, and until discharge)
- Hospital LOS
- Functional outcomes as measured by:
    - distance walked in feet
    - 2011 Knee Society Scores

**Primary Safety Endpoints**:

- Wound infections within 90 days of the date of surgery
- Device related adverse events within 90 days of the date of surgery

**Randomization**:

Subjects will be randomly assigned by a 1:1 ratio to either:

3. **Unipolar electrocautery system** (Covidien ForceTriad™ Electrosurgical System)

4. **Saline-coupled bipolar sealer** (Aquamantys System™ Medtronics)

The Biostatistics Unit will develop a randomization procedure using a permuted block design and the randomization process will occur in REDCap using the Randomization Module. Details, including required record keeping and a well documented single-blind randomization procedure, will be further developed upon approval of this protocol.

**Intention to Treat (ITT)**:

The primary analyses will be based on the ITT population. The ITT population will be defined as any subject who is randomized, regardless of which system is used.

**Interim Analysis and Early Stopping:**

There will be no interim analysis.

**Statistical Methods:**

The test for non-inferiority will be carried out using a 2-tailed 95% confidence interval for the difference ($\delta$ = Unipolar electrocautery system - Saline-coupled bipolar sealer) in the estimated blood loss between the two groups. $\delta$ is the margin of inferiority and will be set at 200 cc. If the upper confidence limit $< \delta$ ($\geq\delta$) then we will conclude that the Unipolar electrocautery system is non-inferior (inferior) to the Saline-coupled bipolar sealer.

This test for non-inferiority will only be performed for the primary study endpoint of estimated blood loss; all other secondary variables will be tests of superiority of Unipolar electrocautery versus Saline-coupled bipolar sealer.

A mixed models repeated measures (MMRM) analysis of variance will be performed separately for hemoglobin and hematocrit, to determine whether the two groups behave differently across time (pre-op, post-op day 0, post-op day 1, post-op day 2, and until discharge). The models will contain one repeated (within subjects) factor of time, a between factor of group, and a group-by-time interaction term. Time will be treated as a fixed effect in the model and an unstructured covariance approach will be used. Results will be reported as adjusted (least squares) means and standard errors. For all analyses, the standard assumptions of Gaussian residuals and equality of variance will be tested. If the standard assumptions are not met, a transformation will be performed, and the results will be brought back to the original units and reported as geometric means with their corresponding lower and upper confidence limits.

LOS (or "Time to discharge from hospital") will be analyzed by applying standard methods of survival analysis, i.e., computing the Kaplan-Meier product limit curves, where group (Saline-coupled bipolar sealer vs. Unipolar electrocautery system) will be the stratification variable. In cases where the endpoint event, "discharge from hospital", did not occur, the number of days until last follow-up will be used and considered 'censored'. These two groups will be compared using the log-rank test. The median "time to discharge from hospital" and corresponding 95% confidence intervals for each group will be obtained from the Kaplan-Meier/Product-Limit Estimates.

A two-sample t-test or Mann-Whitney test will be used to compare the two groups for perioperative blood loss and Functional outcomes (i.e. distance walked, Knee Society Scores). Estimated blood loss will be calculated using the Gross' Formula. The chi-square test or Fisher's exact test, as deemed appropriate, will be used to compare the two groups for wound infections and device related adverse events.

A result will be considered statistically significant at the $p<0.05$ level of significance. All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

# 15 Medical Device Reporting

This clinical trial is designed to compare two commercially available medical devices commonly used in surgical procedures. These devices are being used according to the manufacture's guidelines.

This study will adhere to the adverse event reporting regulations of the Centers for Devices and Radiological Health (CDRH), part of the Food and Drug Administration (FDA) regulations. In accordance with the Safe Medical Devices Act of 1990 (SMDA) (Public Law 102-629) (21 CFR 803.32 (c)) ambulatory surgery centers, hospitals, outpatient diagnostic centers and other user facilities are required to report all incidents in which a medical device or user error may have caused or contributed to the death, serious injury or serious illness of a patient (Appendix K).

## *15.1 Serious Injury or illness definition*

"Serious injury or illness" means those injuries that are life threatening, result in permanent body function impairment or permanent damage to a body structure, or necessitate immediate medical or surgical intervention to prevent permanent body function impairment or permanent damage to a body structure (21 CFR 803.3) (r).

A device may have "caused or contributed to" a patient's death or serious injury, if the death or serious injury was or may have been attributed to the device or the device may have been a factor in the death or serious injury because of:

- Device failure
- Malfunction
- Improper or inadequate device design
- Manufacture
- Labeling or
- User error

## *15.2 Mandatory Medical Device Reporting*

The Medical Device Reporting (MDR) regulation (21 CFR 803) contains mandatory requirements for manufacturers, importers, and device user facilities to report certain device-related adverse events and product problems to the FDA. The regulation specified that reports be filed on FDA Medwatch Form 3500A or an electronic equivalent.

**Device User Facility Reporting Requirements of Serious Adverse Events:**
A "device user facility" is a hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility, which is not a physician's office.

All deaths and serious injuries to which the device has or may have caused or contributed will be reported to the IRB, FDA and the manufacturer.

The user facility will also submit annual reports to the FDA by January 1 of each year as described in 21 CFR 803.33.

Form 3419 Annual User Facility Report

- Medical Device Reporting Annual User Facility Report - Form FDA3419
- Instructions for Completing the Medical Device Reporting Annual User Facility Report, Form FDA3419

**The following "Mandatory Reporting Requirements for User Facilities" will be applicable for this clinical trial:**

| REPORTER | WHAT TO REPORT | REPORT FORM # | TO WHOM | WHEN |
|---|---|---|---|---|
| User Facility | Device-related Death | Form FDA 3500A | FDA & Manufacturer | Within 10 work days of becoming aware |
| User Facility | Device-related Serious injury | Form FDA 3500A | Manufacturer. FDA only if manufacturer unknown | Within 10 work days of becoming aware |
| User Facility | Annual summary of death & serious injury reports | Form FDA 3419 | FDA | January 1 for the preceding year |

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***. Any non-serious adverse event felt to be related to the study device will be captured in the source documents and case report form.

***Adverse Event Reporting Period***

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 2 months from the date of the surgical procedure.

### *15.3 Recording of Adverse Events*

Information on all device related serious and non-serious adverse events will be recorded in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All devices related serious and non-serious 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 determined that the study treatment or participation is not the 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 after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

#### 15.3.1 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB according to their policies. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder.

#### 15.3.2 FDA Notification by Sponsor

This section is not applicable as this is an investigator initiated study.

### *15.4 Unblinding Procedures*

The patient can be unblinded to the treatment arm by the Principal Investigator if this information is necessary for the patient's postoperative care.

### *15.5 Data and Safety Monitoring*

#### 15.5.1 Data and Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of all adverse events deemed related to the medical device. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The PI and nurse research coordinator will monitor safety and review adverse events for subjects enrolled every 2 months. The PI will prepare a safety report for these regular reviews comprised of adverse events and the actions taken. The study protocol will be carried out in accordance

with OHRP/FDA/NIH guidelines and requirements. In the event of a serious adverse event during the study protocol, it will be reported immediately to the PI. Serious AND Unanticipated AND possibly, probably or definitely related AEs will be reported to the IRB within 48 hours of the event by the principle investigator as well as to all members of the research team. Data including all recorded adverse events will also be reviewed to determine if aspects of the study need to be changed or stopped. In addition, the PI will review any and all deviations, adverse events and unanticipated problems that may occur to determine their relatedness to the study, their severity, and whether they require study changes. In addition, any unanticipated problems will be reported to the IRB as per their specific reporting requirements. Anticipated deviations will be submitted to the IRB for approval as a protocol exception prior to its initiation, unless required to eliminate apparent immediate hazards.

# 16 Data Handling and Record Keeping

## *16.1 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 (i.e. that the subject is alive) at the end of their scheduled study period.

## *16.2 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, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

### *16.3 Case Report Forms*

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

The REDCap software will be the electronic CRF used for this study. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Biostatistics Unit of the Feinstein Institute for Medical Research. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at the Feinstein and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Northwell Health researchers by our Clinical Research Service, Research Compliance Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports 1,244 active institutional partners and other institutions in 87 countries (www.project-redcap.org).

Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

## 17 Study Monitoring, Auditing, and Inspecting

### *17.1 Study Monitoring Plan*

This section is not applicable for this study.

### *17.2 Auditing and Inspecting*

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

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

## 18 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator.

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. See Appendix L for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

## 19 Study Finances

### *19.1 Funding Source*

There is no outside funding for this study.

### *19.2 Conflict of Interest*

The investigators have no conflict of interest to report.

### *19.3 Subject Stipends or Payments*

The laboratory tests collected in this study are tests done as standard of care for all orthopedic surgical patients.

There will be no payment to the patients for enrollment in the study.

## 20 Publication Plan

Investigators intend to publish the results of this study. Any published results will only include an aggregate of de-identified data. No protected health information will be disclosed outside of Northwell Health for the purposes of this research.

Protected health information may be shared with:

- The Institutional Review Board (IRB) at Northwell Health Hospitals;
- Doctors and staff at the hospital where this research study will take place;
- Doctors and staff at other institutions that are participating in the research study;
- Governmental entities that have the right to see or review your protected health information, such as the U.S. Office of Human Research Protections and the FDA.

Protected health information will only be used and/or given to others to perform this research; to study the results; and to determine if the research was done correctly. All reasonable efforts will be made to maintain confidentiality (in accordance with the measures outlined above).

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Appendix:

A. Aquamantys Pump Generator User Guide
B. Covidien ForceTriad™
C. Association of Surgical Technologists (AST) Standards of Practice for Use of Electrosurgery
D. Northwell Electrosurgical Safety Policy
E. The Knee Society Score
F. Provider: Medications that require discontinuation prior to joint replacement surgery
G. Patient: Medications that require discontinuation prior to joint replacement surgery
H. Tranexamic Treatment Guidelines
I. Thromboprophylaxis Algorithm
J. ASA classification

K. CDRH Guidance device AE reporting
L. Subject Informed Consent Form