A prospective, randomized, single-blinded superiority study to evaluate bone wax use for hemostasis during primary unilateral total knee arthroplasty

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Cover	Addition of NCT number	

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1. STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A prospective, randomized, single-blinded superiority study to evaluate bone wax use for hemostasis during primary unilateral total knee arthroplasty
Study Description:	Total joint arthroplasty can result in significant blood loss. Postoperative anemia has been associated with prolonged length of stay and increased hospital costs.[1] Minimizing blood loss has led to multiple blood conservation strategies in orthopaedic procedures. Bone wax is a well-known topical hemostatic agent comprised of a mixture of beeswax, paraffin, and isopropyl palmitate. This inexpensive agent works by sealing the bleeding site and tamponades bleeding from the cancellous bone. Bone wax can be precisely applied evenly and stops bone bleeding immediately upon application.[2] The purpose of this study is to assess whether the application of bone wax to exposed cancellous bone, after the cemented implants are in place, will provide superior hemostasis in total knee arthroplasty (TKA) patients compared to patients who do not have the bone wax applied. Hemostasis will be assessed by calculating blood loss using the Hb-balance formula.

	This will be a prospective, randomized, single-blinded, superiority 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.
Objectives:	*Primary Objective:* • Efficacy: To assess whether bone wax results in superior hemostasis in patients undergoing primary unilateral TKA • Safety: To compare the safety profile between the 2 cohorts *Secondary Objective:* • To assess whether the objective and functional outcomes in patients undergoing primary unilateral TKA differ between the patient cohorts (use of bone wax vs no bone wax) • To assess if there is a difference in the reduction of the Hemaglobin (Hgb) and Hematocrit (Hct) between the patient cohorts
Endpoints:	*Endpoints-Primary:* ● Efficacy: To calculate estimated perioperative blood loss on POD 1 using the Hb-balance formula ● Safety: To assess the patients for any device adverse events related to the use of bone wax *Endpoints-Secondary:* ● To calculate the Knee Society Scores (KSS), both objective and subjective scores, done preoperatively and 8 weeks postoperatively ● To measure the difference between the preoperative and POD1 Hemoglobin (Hgb) and Hematocrit(Hct) values in the two patient cohorts

Study Population:	100 female and male patients (50 subjects in each arm) scheduled for unilateral total knee arthroplasty by Drs. Krauss or Segal
Phase:	NA
Description of Sites/Facilities Enrolling Participants:	Department of Orthopaedics, Syosset Hospital
Description of Study Intervention:	Bone wax is a well-known topical hemostatic agent comprised of a mixture of beeswax, paraffin, and isopropyl palmitate. This inexpensive agent works by sealing the bleeding site and tamponades bleeding from the exposed cancellous bone.[2]
Study Duration:	The study timeline is 18 months
Participant Duration:	Patients will be in the study from the date of consent until their 8 week postoperative visit.

1.2 SCHEMA

Preoperative Period — Consent

Total n=100 (50 subjects in each arm)
Preoperative Knee Society Score
Obtain informed consent
Collect Baseline Laboratory Values (Standard of Care)
Screen potential participants by inclusion and exclusion criteria

Day of Operation — Randomization

Confirm Inclusion/Exclusion Criteria
Group 1-Bone Wax (n=50)
Group 2-No Bone Wax (n=50)

Hospitalization — Baseline assessments/ Study Intervention

Complete Blood Count (CBC) (Standard of Care lab)
Calculation of
Device Adverse Event Assessment

Postoperative 8 week — Follow-up assessments of study endpoints and safety

Postoperative KSS
Device Adverse Event Assessment

8 week follow-up phone

Follow-up Telephone Call (Standard of Care)

1.3 SCHEDULE OF ACTIVITIES (SOA)

VISIT WINDOW	PREOPERTIVE PERIOD	DAY OF SURGERY	HOSPITALIZATION	8 WEEK PO VISIT (SOC)	2 MONTH FOLLOW-UP PHONE CALL (SOC)
CONSENT	X				
DEMOGRAPHICS	X				
PRESURGICAL TESTING HISTORY & PHYSICAL (SOC)	X				
PREOPERATIVE KNEE SOCIETY SCORE	X				
CONFIRM INCLUSION/EXCLUSION	X				
RANDOMIZATION		X			
SURGEON TO GRADE AMOUNT OF EXPOSED BONE		X			
DAILY HGB/HCT (SOC)			X		
POSTOPERATIVE KNEE SOCIETY SCORE				X	
DEVICE ADVERSE EVENTS		X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Total joint arthroplasty can result in significant blood loss. Bone wax is a well-known topical hemostatic agent comprised of a mixture of beeswax, paraffin, and isopropyl palmitate. This inexpensive agent works by sealing the bleeding site and tamponades bleeding from the exposed cancellous bone. [2]

The purpose of this study is to assess whether the application of bone wax to the exposed cancellous bone, after the cemented implants are in place, will provide superior hemostasis in a total knee arthroplasty patients compared to patients who do not have the bone wax applied. Hemostasis will be assessed by calculating blood loss using the Hb-balance formula.

This will be a prospective, randomized, single-blinded, superiority 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. The application of bone wax to the exposed cancellous bone has been the standard of care for four years by Drs. Krauss and Segal. The surgeons technique is to apply the bone wax to the exposed cancellous bone after the implant has been cemented in place thereby eliminating the risk for any issues with bone ingrowth.

2.2 BACKGROUND

Postoperative anemia has also been associated with prolonged length of stay and increased hospital costs.[1] In order to minimize blood loss, multiple blood conservation strategies have been developed for orthopaedic procedures. One method of hemostasis in use at Syosset hospital since March 2013 is the use of intravenous antifibrinolytics (tranexamic acid). Tranexamic acid (TXA) interferes with clot breakdown. The administration of tranexamic acid has been associated with a significant reduction of postoperative bleeding and blood transfusions in patients undergoing total joint arthroplasty and has become a well-established practice in orthopaedic surgery. Porter, et al in a 2020 retrospective chart review of 38,220 patients administered intravenous tranexamic acid (IV TXA) found no significant difference in the odds of adverse outcomes (PE,DVT, MI,CVA) between high-risk patients who received TXA and high-risk patients who did not receive TXA. However, one of the limitations of the study was that high-risk patients who did not receive TXA had a higher baseline incidence of risk factors such as DVT,PE, MI, and CVA compared to the high risk patients who did receive TXA.[3] This manuscript was the basis for the current departmental protocol for the administration of TXA. As per this protocol IV TXA is typically not administered to patients with multiple risk factors for thromboembolic events and they are instead given intra-articular TXA by the orthopaedic surgeon Patients excluded from IV TXA will not be enrolled in this clinical trial so as to eliminate any confounding factors. (Appendix A-Total Joint Arthroplasty Pharmacologic Protocols)

Epidural or spinal anesthesia (neuraxial blockade) has been shown to be effective in reducing intraoperative blood loss. Rodgers, et al in a meta-analysis of 473 patients in 16 trials reported the requirement for a transfusion of two or more units of blood was reduced by about half in patients allocated to neuraxial blockade.[4] 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.

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 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.

Significant blood loss intraoperatively and post-operatively can produce complications. The use of hemostatic agents such as bone wax may further facilitate hemostasis during a total knee arthroplasty. Bone wax was developed in 1885 by a British neurosurgeon named Sir Victor

Horsley. Bone wax consists of beeswax, paraffin and isopropyl palmitate. Since its first documentation of hemostatic potential in 1892, there has been a number of modifications to its formulation.[2] The main component that remains is beeswax. Today bone wax is used in a variety of surgical procedures as a mechanical hemostatic agent. During total joint arthroplasties bone wax is softened and applied firmly on the cancellous bone around the prostheses.

Bone wax increases hemostasis because of its ability to immediately seal and plug marrow sinusoid and consequently prevent oozing of blood.[3] Studies have shown other benefits of bone wax, like the ability to decrease post-operative edema and pain.[5] In the study conducted by Moo et al. 100 patients were recruited into a 1:1 randomization: (1) bone wax (2) control. Measurements were taken for height, weight, serum hemoglobin levels and base line lower limb diameters. Hemoglobin (Hgb) and Hematocrit (Hct) levels were checked on POD 1 and POD 3. Each study subject underwent total knee arthroplasty using standard procedures. Bone wax was applied around the prosthesis to obtain hemostasis in these areas. A significant decrease in blood loss was observed in the bone wax group at POD 1 and 3. None of the patients in the bone wax cohort required blood transfusions. Three patients in the control group required a blood transfusion.[2]

The limitations in the Moo et al. study were, they did not collect postoperative outcomes such as pain, range of motion, and Knee Society Score (KSS). Efficacy and safety data are lacking in this publication as most patients were transferred to a rehabilitation facility. Long term follow-up on clinical outcomes such as range of motion and functional assessment scores were not reported. The study subjects consisted of patients with osteoarthritis of the knee only, thereby, excluding whether patients with other inflammatory arthritis may benefit from the use of bone wax. The use of a chemical hemostatic agent tranexamic acid (TXA) was also excluded from the surgical procedure. The incorporation of TXA could have increased the level of hemostasis.

A recently published manuscript by Shin, et al also evaluated blood loss outcomes with the use of bone wax. Though this study also found bone wax reduced blood loss there were several limitations to the study. First, its retrospective design is inherently disadvantageous. Second, the postoperative outcomes such as pain score, range of motion, length of stay and clinical scores, were not comparted between the groups. Third, although there was no significant intergroup difference in the radiologic prosthetic coverage of the osteotomy surface, the area of the cancellous bone surface uncovered by the femoral and tibial components were not evaluated intraoperatively. The area of residual osteotomy might be associated with the volume of blood loss and consequently with transfusion rates because osseous hemorrhage is one of the main bleeding sources.[5]

The investigators would like to address limitations in these studies by conducting a prospective, randomized trial. This study will also be collecting outcome measures (Knee Society Score) which were noted limitations of these studies. Additionally, the surgeons will be measuring the amount of exposed cancellous bone in the OR. The method to be used is referenced in this protocol.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The surgical techniques used to promote hemostasis will be consistent for all patients, except for the use of bone wax applied to the exposed cancellous bone following insertion of the prosthesis. There is a potential that patients in the control arm could have increase bleeding. The following risks have been shown to be associated with the use of bone wax: failed bone healing, foreign body reaction, granuloma growth, thrombosis, infection, and nerve compression

There is a small risk of an unintended breach of confidentiality, as there is in any research study that collects subjects' health information.

2.3.2 KNOWN POTENTIAL BENEFITS

Bone wax is used on cancellous bone to reduce blood loss during orthopaedic surgery. The incorporation of this hemostatic agent in standard TKA procedures could lessen the total blood loss intra-operatively and postoperatively for patients randomized to the study group.

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

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Shin and Moo have published on the use of bone wax in total knee arthroplasty, 296 and 50 patients respectively had bone wax used during their total knee replacement. Shin, et al found that no adverse reactions, including the development of infections or foreign body reactions, were observed after the application of bone wax, a finding consistent with those of Moo et al. [5]

Moo found the difference between the bone wax group and the control group with regards to transfusion requirements and adverse events following surgery did not reach significance with the numbers available; however, trends in favor of the use of bone wax were noted.[2]

Drs. Krauss and Segal have been using bone wax on exposed cancellous bone for over 4 years. All surgical site infections are reported as part of the Northwell Health System quality metrics. Bone wax has been used in 1140 total knee procedures. For this time period superficial

infections were reported in 2 patients and 1 deep infection. Additionally, the surgeons have not had any other issues felt to be related to the bone wax in their patients during their long term follow-up visits. The surgeons technique is to apply the bone wax to the exposed cancellous bone after the implant has been cemented in place therefore eliminating the risk for any issues with bone ingrowth.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
• Efficacy: To assess whether bone wax results in superior hemostasis in patients undergoing primary unilateral TKA	• To calculate estimated perioperative blood loss on POD 1 using the Hb-balance Formula	Use of the Hb-balance Formula provides a more accurate assessment of blood loss
• Safety: To compare the safety profile between the 2 cohorts	• To assess the patients for any device adverse events related to the use of bone wax	To ensure there are no safety issues between the two cohorts

Secondary		
• To assess whether objective and functional outcomes in patients undergoing primary unilateral TKA differ between the two patient cohorts	• To calculate the Knee Society Scores, both objective and subjective scores, done preoperatively and 8 weeks postoperatively	The Knee Society Score is a validated tool to assess both objective and subjective outcomes. The collection of the KSS is a standard of care for Drs. Krauss and Segal's TKA patients.
• To determine if there is a difference in blood loss between the two cohorts	• To measure the difference between the preoperative and POD1 Hemoglobin (Hgb) and Hematocrit (Hct) values in the two patient cohorts	These values will be used to assess hemostasis over time

4 STUDY DESIGN

4.1 OVERALL DESIGN

- ***A statement of the hypothesis:*** The use of bone wax on exposed cancellous bone surfaces will provide superior hemostasis.
- ***Phase of the trial:*** NA. This study is using a FDA approved marketed product as per the package instructions.
- ***A description of the type/design of trial to be conducted****:* A prospective, randomized, single-blinded superiority study to evaluate bone wax use for hemostasis during primary unilateral total knee arthroplasty.
- ***A description of methods to be used to minimize bias:*** All patients scheduled for unilateral total knee arthroplasty will be approached for inclusion in the study.

- ***The number of study groups/arms and study intervention duration:*** This study will consist of 2 cohort groups. One group (50 patients) will have bone wax applied to the exposed cancellous surfaces of the bone (treatment group). The other group (50 patients) will serve as a control group. This study is a 1:1 allocation ratio. The patients will not be aware of their randomization assignment.
- ***Indicate if single site or multi-site:*** Single Site-Syosset Hospital Department of Orthopaedics

- ***Name of study intervention(s):*** Bone Wax
- ***Note if interim analysis is planned and refer to details****:* No interim analysis is planned.
- ***Note if the study includes any stratifications:*** Patient stratification is not needed for the randomization.
- **Name of sub-studies, if any, included in this protocol:** Not Applicable

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The investigators would like to address limitations in the studies done by Moo and Shin by conducting a prospective, randomized trial.

This study is designed to assess if applying bone wax to exposed cancellous bone during total knee arthroplasty provides superior hemostasis. Patients will be randomized to receive bone wax (treatment group) or no bone wax (control group). Blood loss will be calculated using the Hb-balance Formula to provide a consistent measurement of perioperative and postoperative bleeding. All other standard of care intraoperative blood minimizing strategies will be consistent for these patients. These strategies include pneumatic tourniquet, intravenous tranexamic acid, and spinal anesthesia. The Inclusion/Exclusion criteria were developed to ensure this consistency.

Objective and functional outcomes will be obtained using the 2011 Knee Society Score (KSS). The KSS will be completed preoperatively and postoperatively at the 8 week visit, or the visit closest to this time point., (Appendix B- Preoperative/Postoperative 2011 Knee Society Scores)

Preoperatively patients taking anticoagulants or antiplatelets, with the exception of aspirin 81 mg daily, 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 who are unable to stop these products for any reason will be excluded from the study.

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.

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 or Dr. Segal if the date of the original consent is greater than 30 days from the date of surgery. The inclusion and exclusion criteria will be verified prior to study randomization using the laboratory testing done in Pre-surgical Testing (PST) and the preoperative medical history documents. Patients will be randomized to either the treatment group (bone wax) or the control arm (no bone wax). The operating room (OR) staff will be notified of the treatment arm.

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, as per standard of care and department treatment guidelines.

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 use of bone wax 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. Hgb and Hct are drawn daily during the patient's hospitalization as per the standard of care. These values will be used to calculate the Hb-balance Formula.

Blood loss will be calculated using the Hb-balance Formula. 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.[7]

Following discharge patients will be followed in the outpatient surgical office according to the postoperative standard of care visit schedule. Results of the 2011 KSS Objective and Functional Outcome Measurements administered as part of standard of care at the 8 week postoperative visit, or the office visit closest to these time points will be collected for research purposes. Patients will be called at 56 days (+2weeks) from the date of surgery for any device related adverse events. This call is standard of care for the department. Three attempts will be made to reach the patient before they are considered "lost to follow-up".

4.3 JUSTIFICATION FOR DOSE

Not Applicable

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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. Patient willing to complete all study related procedures

5.2 EXCLUSION CRITERIA

1. Patients unable to take aspirin or apixaban for VTE prophylaxis

2. Allergy to any of the ingredients in bone wax (beeswax, paraffin, or isopropyl palmitate)

3 . Patients taking clopidogrel (Plavix), ticagrelor (Brilinta), or prasugrel (Effient) or any other antiplatelet medication (except for aspirin 81 mg)

4. Patients unable to get IV TXA for any reason

5. Patients requiring anticoagulant treatment prior to surgery

6. Any medical condition that in the opinion of the investigator would require special fluid management protocols during or after surgery

7. Allergy to TXA

8. Blood transfusion within 1 month of surgery

9. Patients who are unwilling to undergo blood transfusion, if necessary

10. Patients who have habitual opioid use

11. Patients who have a psychiatric or mental illness which could impair the consent process or ability to complete patient-reported questionnaires

12. Fixed motor deficit affecting functional assessment of the knee

13. Patients with a contraindication to spinal anesthesia

14. Patients receiving erythropoietin therapy for anemia

15. 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

16. Patients with a contraindication for the pneumatic tourniquet applied in the operating room

5.3 LIFESTYLE CONSIDERATIONS

There are no lifestyle modifications or requirements for this study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participation in the clinical trial will be discussed with the patient by Dr. Krauss, Dr. Segal, or a designee, when the patient is first scheduled for a unilateral 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

Consent will be obtained at any time during the preoperative period. The patients will be provided with contact information for the research staff for any questions or concerns.

This study will not be including any vulnerable or cognitively impaired patients.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Bone Wax is commercially available and is being used in accordance with approved labeling. During total joint arthroplasties bone wax is softened and applied firmly on the exposed cancellous bone around the prostheses by the orthopaedic surgeon after implant cementing. . (Appendix C-Bone Wax Package Insert)

6.1.2 DOSING AND ADMINISTRATION

Bone wax should be used immediately after removal from the package. Softened Bone Wax is applied to the bone edges as indicated by the surgical circumstances and the preference of the surgeon. Exposed cancellous bone surface can vary between patients. In order to capture this variance the surgeons will calculate the amount of exposed bone by the following method:

Once the distal femoral cut and prep for the chamfer cuts and notch cut is complete:

1. Measure the distal femur medial to lateral (ML) distance.
2. Measure the distance from anterior chamfer to most proximal portion of exposed anterior femoral bone.
3. Measure the ML distance of anterior chamfer.
4. Measure the height of the notch cut, meaning, the anterior posterior (AP) distance (notch surface).

Those measurements will be collected as well as the femoral implant size.

Calculations of surface area:

1. ML surface - will be calculated as ML distance - ML width of the implant. That number, will be than be multiplied by the combined length of the implant distal condyl and anterior chamfer.
2. Anterior surface - which is mostly a triangle shaped will be calculated as, ML distance of anterior chamfer (triangle base) times the triangle height which is distance from anterior chamfer edge to most proximal exposed bone on the anterior cut divided by 2. From that surface area, the implant anterior flange area will be deducted.
3. Notch surface - will be calculated as AP notch height X width of the notch. For implant size 2-5 there is the same notch width, and 6-10 have same notch width.

Combining the value of 1+2+3, is the overall exposed bone surface that needs bone wax coverage.

The exposed bone surface will be document by following grading system:

Grade 1: up to 3 millimeters (mm) of exposed bone
Grade 2: >3 to 6 mm exposed bone
Grade 3: >6 mm exposed bone

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Not Applicable

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Bone wax is a sterile mixture of beeswax, paraffin, and isopropyl palmitate. It is opaque and has a waxy odor. Bone wax is available sterile in individual foil envelopes.

6.2.3 PRODUCT STORAGE AND STABILITY

No special storage conditions are required.

6.2.4 PREPARATION

Using aseptic technique, Bone wax should be warmed to desired consistency by manipulation with the fingers.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The Biostatistics Unit will develop a randomization procedure using a permuted block design within the Biostatistics Randomization Management System (BRMS) system. Additional details of the procedure, including required record keeping, will be further developed upon approval of this protocol. The Biostatistics Unit has extensive experience in implementing and in producing detailed documentation for such procedures. The patient will be blinded to their randomization group.

6.4 STUDY INTERVENTION COMPLIANCE

The surgeon and the operating room staff will be notified of the treatment arm prior to the start of the surgery. All patient outcome measurements are part of the standard of care for a total knee arthroplasty patient.

6.5 CONCOMITANT THERAPY

Not Applicable

6.5.1 RESCUE MEDICINE

Not Applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Not Applicable

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. All analyses will be carried out according the ITT principle. The ITT population will be all patients randomized, regardless of whether or not treatment wax administered. All patients will be analyzed in the group to which they were randomized.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- A medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded in REDCap.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the scheduled postoperative visits and is unable to be contacted by the site staff after 3 attempts.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

This clinical trial does not require any study specific screening tests or procedures. Preoperative screening done as part of the standard of care for an arthroplasty patient will be used to determine patient inclusion and exclusion. Additionally, there are no required lab testing or procedures required for this clinical trial.

Following discharge patients will be followed in the outpatient office according to the postoperative standard of care visit schedule. The 2011 KSS Objective and Functional Outcome Measurements will be collected at the 8 week visit, or the office visit closest to these time points. Patients will be contacted via phone approximately 56 days from the date of surgery to capture any device related adverse events or other relevant patient outcomes. These KSS outcomes measures and follow-up phone calls are standard of care for the department.

8.2 SAFETY AND OTHER ASSESSMENTS

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.
Medical Device Reporting:

This clinical trial is evaluating a commercially available marketed product. This product is 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.

Adverse Event Reporting Period

The study period during which adverse events must be reported is defined as the period from the application of the bone wax to the end of the study treatment follow-up.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

8.3.3 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

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

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.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention (device) assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

This clinical trial consists of postoperative total knee arthroplasty patients. DRE's common and expected in this group of patients include postoperative pain, nausea, hypotension, anemia, and dehydration. Events anticipated and expected in the postoperative arthroplasty patient will not be considered an adverse event for collection in the eCRF. Additionally, there are no study interventions for the control group. This group will be following the standard of care treatment for a total knee arthroplasty patient. Therefore, no adverse events related to the application of bone wax will be occurring in this group.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 5 working days after the investigator first learns of the effect. The investigator is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA). Thereafter, the investigator shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not Applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not Applicable

8.3.9 REPORTING OF PREGNANCY

Not Applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).]

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 5 working days of the investigator becoming aware of the event.

- Any other UP will be reported to the IRB within 5 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB decision.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not Applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

The primary endpoint is estimated total blood loss measured on POD 1, as calculated by Hb-Balance formula. Blood loss is measured in the morning prior to receiving anticoagulant treatment. We hypothesize that applying bone wax during TKA will reduce blood loss on POD 1.

- Secondary Efficacy Endpoint(s):

The secondary endpoints are hemoglobin and hematocrit from preoperative to POD 1, as well as, the Knee Society Score (KSS), which is collected preoperatively and 8 weeks postoperatively. There are two KSS scores; namely, (1) the patient's self-assessment of pain, expectations and functional outcomes, as well as, (2) the surgeon's objective measurements.

We hypothesize that applying bone wax during TKA will reduce the quantity of change in hemoglobin and hematocrit from preoperative to POD 1.

We hypothesize that applying bone wax during TKA will positively impact KSS; namely, a reduction in pain, an increase in functional outcomes and an increase in alignment, range of motion and stability at 8 weeks postoperative.

9.2 SAMPLE SIZE DETERMINATION

Our study will include 50 subjects in each arm (i.e., 100 subjects in total), which is based on feasibility and availability of resources. However, if a formal power calculation were to be conducted using a two-sample t-test at a significance level of 0.05, a sample size of 100 subjects would be more than sufficient to detect a difference in mean blood loss of about 150 mL to 200 mL between the control group and the treatment group, which the investigators consider to be clinically significant. The table below shows different scenarios for higher and lower mean blood loss, as well as, scenarios with a larger standard deviation. The assumed pooled standard deviation derived from the study by Moo et al was 271.5 (the standard deviations of the control and bone wax groups in the study were 282.7 mL and 259.8 mL, respectively).

Mean Blood Loss POD 1 Difference (control - bone wax)	Pooled Std Dev	Power
153	271.5	80%
200	271.5	95%
175	300.0	82%
200	300.0	91%
200	350.0	81%

9.3 POPULATIONS FOR ANALYSES

All analysis will be conducted on the intention-to-treat (ITT) population. The ITT population is defined as all randomized participants analyzed in the group to which they were randomized, regardless of the treatment received.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics (mean, standard deviation, frequencies and percentages) will be used to describe the baseline clinical and demographic characteristics of the sample. The treatment and control groups will be compared using formal statistical tests on all other outcomes.

All analyses will be considered significant at $p < 0.05$ and conducted in SAS v. 9.4 (SAS Institute, Inc., Cary, NC).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Estimated total blood loss on POD 1 will be compared between the treatment and control groups using a two-sample t-test. If the standard assumptions of Normally distributed residuals and equality of variance do not hold, then an appropriate transformation or non-parametric method will be used.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Separate linear mixed models for repeated measures will be used to compare each secondary outcome of interest (hemoglobin, hematocrit and KSS) between the treatment and control groups over time from preoperative to postoperative. An appropriate transformation will be used for any outcome that does not meet standard assumptions of Normality.

9.4.4 SAFETY ANALYSES

Adverse events will be reported descriptively as the amount of adverse events are expected to be minimal.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Not Applicable

9.4.6 PLANNED INTERIM ANALYSES

Not Applicable

9.4.7 SUB-GROUP ANALYSES

Not Applicable

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not Applicable

9.4.9 EXPLORATORY ANALYSES

Not Applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their

records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB). Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. . Research data will be stored in Northwell REDCap and the code key will be stored in a research ePHI folder on Northwell server.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB Institutional policies.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not Applicable

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator
Eugene Krauss,MD,FAAOS,FACS
Syosset Hospital, Northwell Health
221 Jericho Turnpike
516-496-2637
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Steering Committee, Executive Committee, Subcommittee are not applicable for this study.

10.1.6 SAFETY OVERSIGHT

The principal investigator will review safety data in aggregate when overall enrollment reaches 30 subjects and 60 subjects.

10.1.7 CLINICAL MONITORING

Not Applicable

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data, including agent related adverse events (AEs), data will be entered into REDCap system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study document will be retained for 10 years following study termination.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

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.

10.1.12 CONFLICT OF INTEREST POLICY

Eugene Krauss and Ayal Segal, the study doctors, receive financial support from DJO Global, the company that is involved in this study. The money this study doctor receives from this company is for work as a consultant and is separate from this study. The study doctors receive no payment for any work related to this study.

10.2 ADDITIONAL CONSIDERATIONS-APPENDIX

Appendix A-Total Joint Arthroplasty Pharmacologic Protocols

Appendix B- Preoperative/Postoperative 2011 Knee Society Scores
Appendix C-Bone Wax Package Insert

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CM	Centimeter
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IV	Intravenous
KSS	Knee Society Score
LOS	Length of stay
LSMEANS	Least-squares Means

MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
POD	Postoperative Day
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
TKA	Total Knee Arthroplasty
TXA	Tranexamic Acid
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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7. Eipe NP, Ponniah M. Perioperative blood loss assessment-how accurate? Indian J. Anaesth. 2006; 50(1):35-38

Appendix:

A. Total Joint Arthroplasty Pharmacologic Protocols
B. Preoperative/Postoperative 2011 Knee Society Scores
C. Bone Wax Package Insert