

APR 13 2010

**PART B  
STUDY DESCRIPTION**

<b>TITLE OF PROTOCOL</b>	<b>Does Ketorolac Delay Bone Healing and Improve Post-operative Pain?: A Prospective Double-Blind Placebo-Controlled Randomized Clinical Trial</b>		
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**B1. PURPOSE OF PROTOCOL**

The purpose of this study is to evaluate the effects of ketorolac (30 mg IV dose intra-operatively followed by 10 mg orally every 8 hours for five days) together with standard of care in pain control, compared to placebo (one pill every 8 hours for five days) plus standard of care, in patients undergoing Kalish bunionectomies. Long-term outcomes of bunionectomy procedures will also be evaluated including radiographic healing, adverse events, and time to regular shoe gear and activities up to a six month period.

**B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY**

**A. Ketorolac and Pain Control**  
**A.1 NSAIDs and Post-operative Bunionectomy Pain Control**

There are several studies which have found analgesic benefits of NSAIDs following bunionectomy procedures. Valdecoxib has been studied in two randomized double-blind placebo-controlled trials following elective bunionectomies (total sample size 852). Valdecoxib was found to significantly reduce post-operative pain, decrease the amount of opioid rescue medication requirements, and increase patient satisfaction (1).

Desjardins and colleagues conducted a randomized, double-blind, placebo-controlled trial where 223 patients either received valdecoxib (20, 40, or 80 mg) or placebo just prior to bunion surgery. Patients randomized to any of the valdecoxib doses experienced less pain and required less supplemental rescue medication (2). Another randomized controlled trial (RCT) by Desjardin and colleagues in 2004 randomized 252 bunionectomies to either rofecoxib 50 mg, diclofenac sodium 100 mg, or placebo. Patients who received rofecoxib or diclofenac sodium were found to have faster onset of pain control, better peak pain relief, and reduced opioid requirements (3). In another study, patients were randomized to IV parecoxib sodium or placebo for 24 hours after bunionectomies. Patients had less pain and required less rescue medication (hydrocodone 5 mg/ acetaminophen 500 mg) in the parecoxib sodium group (4). Parecoxib sodium has also been given 30-45 minutes prior to bunion surgery and was found to significantly reduce post-operative pain over placebo (5).

There are no studies that evaluate the effects of ketorolac together with opioid pain management following bunionectomy procedures. Furthermore, the only study which included ketorolac in

bunionectomy procedures evaluated whether or not IV ketorolac could be added to local anesthetics (6). Finally, bunionectomy studies compared other NSAIDs to placebos as opposed to NSAIDs and how they interact and compare to opioids.

### **A.2 Ketorolac and Post-operative Pain Control**

There have been several publications comparing the pain control benefits of ketorolac versus placebo and other opioid medications in orthopedic surgery. Reines and colleagues randomized 242 patients to either ketorolac, oxycodone plus acetaminophen, or placebo and found that both ketorolac and oxycodone plus acetaminophen groups effectively controlled post-operative pain after orthopedic surgery (7). Many other studies have demonstrated the analgesic benefits of ketorolac (8-15).

Thus far, only one RCT has been published which compares the synergistic relationship of ketorolac with an opioid to the same opioid route and dose in isolation. In this double-blind RCT, ketorolac and 5 mg of intra-venous (IV) morphine were given to the experimental arm, while the control arm was given 5 mg of IV morphine alone. Patients then rated their pain on a 100 mm visual analog scale (VAS). An observed difference of 1.8 on the VAS was reported as statistically significant ( $p < 0.05$ ). The authors emphasize the fact that their findings represent both a statistically and clinically significant difference in pain (16). This is based on work that establishes the minimally clinically relevant difference in pain levels on the VAS is 1.3 (17). Although a well executed industry-free double-blind RCT, the authors note in their limitations that they felt that the study design did not demonstrate the complete efficacy of the synergistic relationship. This is because the ketorolac loading dose used was only 15 mg versus the more standard 30 mg dose. They did this in order to determine the most accurate minimum difference between the groups. In this study, the opioid used was morphine 5 mg IV, which is the equivalent of oxycodone 10 mg orally (18). Because of the universal use of morphine for pain control in industrialized and undeveloped countries, it has become widely accepted to utilize morphine equivalents as a reference for pain control. This relationship permits the authors of this application to make the connection between the Safdar trial and the proposed study medications (16). It should be noted that IV post-operative opioids are not necessary for out-patient bunionectomy procedures. Therefore, studies evaluating the synergistic effects of ketorolac with oral opioids in an out-patient setting are lacking.

### **B. Ketorolac and Bone Healing**

#### **B1. Basic Science Overview**

Although ketorolac has been demonstrated to reduce post-operative pain, this benefit has been over-shadowed by some due to concerns of the potential association between osseous nonunions and ketorolac. Ketorolac is a non-selective nonsteroidal anti-inflammatory drug (NSAIDs) which inhibits the synthesis of cyclooxygenase-1 and cyclooxygenase-2 (COX-1, COX-2). Cyclooxygenase is required for the body to convert arachidonic acid to prostaglandin. Thus, NSAIDs inhibit prostaglandin production and therefore reduce pain and inflammatory responses (19-22).

Some studies have found that prostaglandins play regulatory roles in bone healing, primarily following fractures. Prostaglandins stimulate the differentiation of osteoblasts and osteoclasts, which are both necessary cells during the bone healing process (20, 23-24).

NSAIDs, which inhibit prostaglandins, have been found in animal models and by *in vitro* studies to alter osteoclast and osteoblast differentiation. For these reasons, it is believed that NSAIDs may increase the risk of developing nonunions or delay osseous healing (25-34). However, *in vivo* studies are lacking and knowledge in this area is primarily limited to animal studies.

#### **B2. Clinical Studies Overview**

As the only parenteral non-selective NSAID available in the United States, ketorolac has been evaluated frequently (36). Glassman found a more than fourfold higher proportion of pseudoarthrosis in patients receiving ketorolac than those that did not. In the Glassman study, the overall incidence of nonunion was 11.8% in 288 patients (48.9% of the study population were smokers). Their work was the first clinical trial to propose that NSAIDs, and ketorolac specifically, may delay bone healing

following spinal fusion (37).

Critics of the Glassman paper have cited that smokers made up 48.9% of the study population and thus the difference observed was either due to effect modification with the synergistic detriments of ketorolac and smoking resulting in the observed significant difference of 13.3% between the experimental and control arms. If the observations were limited to non-smokers, the overall incidence drops to 6.8% and the difference between treatment arms becomes 8.9%. This represents an overall reduction of nonunions by 43% and a halving of the difference between ketorolac and controls (37).

Pradhan and associates conducted a study in a similar population as Glassman's but excluded smokers. Of the 405 patients undergoing spinal fusion, Pradhan noted a 0.9% higher rate of pseudoarthrosis in patients without ketorolac versus those who did receive the drug with an overall incidence in 5.67% in a population of non-smokers. They concluded that ketorolac does not negatively impact bone healing. Pradhan's spinal nonunion incidence among nonsmokers of 5.6% does seem to be more consistent with the non-smoking Glassman patients of 6.8%. However, a substantial limitation of this study was that patients in both treatment arms could have received autogenous bone graft. (38).

A 2005 article of 434 subjects compared patients taking no NSAIDs versus ketorolac undergoing spinal fusion with an overall incidence of 11.1%, and 2.6% among non-smokers. Smokers contributed 3.6% of the total population and were relatively balanced in the groups. Among non-smokers, ketorolac users had a 3.4% and controls had a 2.2% nonunion rate. In this same experiment Rofecoxib and Celecoxib were also tested and had a 2.2% and 2.3% respective nonunion rate among non-smokers. Thus they noted that ketorolac may have the potential to inhibit bone healing (39).

Finally, Sucato noted a 1.2% ( $p>0.05$ ) difference in the proportion of patients taking no NSAIDs versus ketorolac undergoing spinal fusion with an overall incidence of 2.5%. Smokers made up 0.6% of the study population and none of them developed a nonunion. Among non-smokers, 1.9% Ketorolac users and 3.1% of controls had a nonunion ( $p>0.05$ ). The overall incidence among non-smokers was 2.5% (40).

To the authors' knowledge, only retrospective reviews evaluating the influence of ketorolac and delayed healing have been conducted in the clinical setting. As noted above, this includes both supportive and antagonistic evidence. Furthermore, ketorolac, as well as other NSAIDs have been primarily studied in spine surgery or studies dealing with traumas and high energy fractures. In all of the studies evaluating NSAIDs and post-operative bunionectomy pain, bone healing was not evaluated, nor reported as a significant adverse event. This is an important distinction to note, since bunion correction involves long bone healing while spinal surgery entails irregular bone healing. Bunionectomy procedures also involve making a controlled osteotomy cut which may biologically vary substantially from traumatic and fusion of two independent bones as is the case with spine arthrodesis.

### **C. Preliminary Studies/Pilot Data**

Review of the investigators' sites revealed that the Kalish bunionectomy has been in use for over 15 years. Ketorolac has been intermittently and randomly administered to patients for approximately ten years. Given there are no contra-indications or dosage adjustments, patients may be given 30 mg intra-venous near the end of surgical case. Patients then begin taking 10 mg orally, every 8 hours for a total of five days post-operatively.

Additional pilot data was undertaken at one of the investigators' outside sites (Mount Auburn Hospital, Cambridge, MA). An IRB approved retrospective chart review evaluated the outcomes of a bunionectomy procedure. Within this study, we determined the incidence of nonunions following a Lapidus bunionectomy. Some of these patients also received ketorolac (30 mg IV intra-operatively, then 10 mg orally for a total of five days). There were 29 patients that underwent a modified Lapidus bunionectomy with at least two lag screws, in 2007-2008 that were also given ketorolac for pain control. Radiographs were assessed for nonunions by utilization of a previously documented scoring

system found to have both high inter- and intra-observer reliability in a series of tibial fractures reduced surgically with serial radiographs. This scoring system grades each fracture according to four characteristics: 1. Rating of fracture healing, 2. Callus morphology, 3. Number of cortices visible or obliterated. 4. Number of cortices bridged (41). The modification utilized for this pilot data was as follows:

- ❖ **Grade 1:** Homogenous bone structure with complete obliteration of fusion site
- ❖ **Grade 2:** Massive bone trabeculae crossing fusion site, 3-4 cortices are bridged with fusion site barely discernable
- ❖ **Grade 3:** Apparent bone trabeculae crossing fusion site, 2-3 cortices are bridged with fusion site discernable
- ❖ **Grade 4:** Trace bone trabeculae crossing fusion site, 1-2 cortices are bridged with distinct visible joint space
- ❖ **Grade 5:** No bone trabeculae crossing fusion site, 0 cortices are bridged with complete visible joint space

Nonunion was defined as grades 4 or 5. Nonunion analysis was performed by two independent foot and ankle surgeons. Both evaluators agreed that there was one nonunion out of 29 cases or 3.45%. This compares favorably with historical controls. According to prior literature, baseline nonunion rates (traditional Lapidus approach, no ketorolac reportedly given) for this procedure ranges between 0-12%, with higher nonunion rates occurring in older literature. It is believed that nonunion rates were higher in older literature due to the use of smaller screw sizes and antiquated surgical techniques (42-50). This pilot data implies that the addition of ketorolac did not appear to have adverse consequences with bone healing in this cohort of patients.

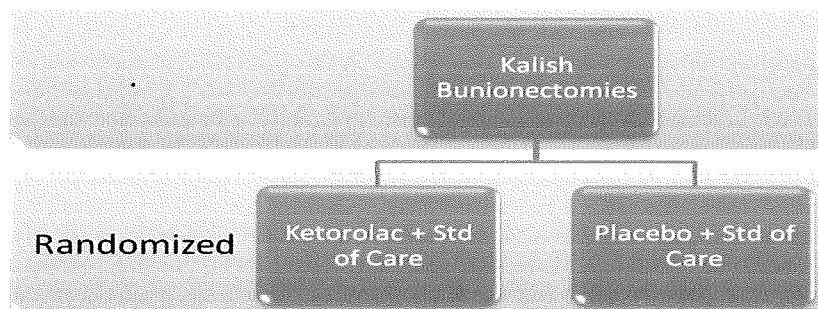
### B3. DESCRIPTION OF RESEARCH PROTOCOL

#### A. Study Design – Overview, Methods, Procedures

##### A.1. Overview

This will be a prospective randomized double-blinded clinical trial that will accept all eligible consecutive patients undergoing elective Kalish bunionectomies (Figure 1). Patients will be randomized into either receiving ketorolac (30 mg IV dose intra-operatively followed by 10 mg orally every 8 hours for five days) plus standard of care or placebo (one pill every 8 hours for five days) plus standard of care. Patients will be assessed for pain via a validated pain questionnaire and for nonunion via a radiographic scoring system that has both high inter- and intra-observer reliability by a blinded assessor (41).

##### Figure 1. Study Overview



The purpose of this study is to evaluate the effects of ketorolac (30 mg IV dose intra-operatively

followed by 10 mg orally every 8 hours for five days) together with standard of care in pain control, compared to placebo (one pill every 8 hours for five days) plus standard of care, in patients undergoing Kalish bunionectomies. Long-term outcomes of bunionectomy procedures will also be evaluated including radiographic healing, adverse events, and time to regular shoe gear and activities up to a six month period.

### **A.2. Patient Standard of Care**

All study participants will receive standard of care for post-operative bunionectomy pain control. A standard amount of pain medication will be prescribed to all study patients. Oxycodone 5 mg – acetaminophen 325 mg will be given to all patients. Patients may take 1-2 tablets every 4-6 hours as needed for pain. Patients will be excluded if he/she has a known allergy or contra-indication to oxycodone or acetaminophen. In the event, an enrolled patient experiences adverse reactions from the standard of care narcotic pain medication (oxycodone 5 mg – acetaminophen 325 mg), this medication will be discontinued and the surgeon may provide substitute medications as deemed necessary. Any deviations from the initially prescribed oxycodone 5 mg – acetaminophen 325 mg, will be recorded and converted to a common scale if necessary.

Monitored anesthesia care (IV sedation) will be provided to all patients during his/her surgery. The anesthesiologist may convert to other forms of anesthesia if he/she deems it is medically necessary during the course of the surgery. The type and amount of peri-operative opioids and anti-emetics given by the anesthesiologist will also be standardized. The peri-operative opioid used will be fentanyl. The fentanyl will be titrated by the anesthesiologist in standard fashion to maintain vital signs (HR and BP within 20 % of preoperative values, and respiratory rate between 10-20. The peri-operative anti-emetic used will be Zofran as that is standard of care for the BIDMC Department of Anesthesiology. The surgeon will also administer pre-operative local anesthetic consisting of 15-20 cc's of 0.5% bupivacaine plain.

### **A.3. Surgical Technique**

The surgical technique outlined here follows the accepted standard technique for a Kalish bunionectomy for all surgeons involved in this study and is also described by Chang TJ in McGlamry's Comprehensive Textbook of Foot and Ankle Surgery (53). All surgeons involved with this study are very experienced with this commonly performed procedure. **There is no surgical technique deviation as a result of this study.**

All patients will receive a preoperative Mayo block consisting of 15-20 cc's of 0.5% bupivacaine plain. Patients with a known allergy to bupivacaine are excluded from the study. A lateral release following the guidelines in McGlamry will be performed to free soft tissue sesamoidal adhesions. Following the lateral release, a capsulotomy will expose the first MTPJ, first metatarsal head, and distal shaft. The medial eminence is then resected being careful to preserve the sagittal groove. A 0.045 inch Kirschner axis guide wire is placed at the apex of the planned offset V-osteotomy, going from medial to lateral in the metatarsal head. The apex sits just below the central point of the metatarsal head to account for the long dorsal arm. The orientation of the axis guide wire accounts for any abnormal metatarsal protrusion distance or sagittal plane deformity. Using a sagittal power saw, a through-and-through offset V-osteotomy is performed going from medial to lateral, keeping the blade parallel to the axis guide wire. One arm of the osteotomy is longer than other arm to allow for screw fixation. The axis guide wire is utilized for proper osteotomy orientation. The capital fragment is then transposed laterally and impacted onto the metatarsal. Once proper alignment is achieved, temporary fixation with Kirshner wires may be used if needed. Two cannulated 3.0 mm partially threaded screws will be placed perpendicular to the osteotomy site from dorsal to plantar. This is the preferred fixation for this

study, however, the surgeon may deviate intra-operatively based on the following guidelines (we do not anticipate any significant surgical technique deviations): failure to achieve adequate compression, intra-operative complication necessitating change in fixation, less than 60-70% of bone-to-bone contact of capital fragment to remaining metatarsal head and shaft, surgeon preference. Any intra-operative deviations will be recorded and accounted for in the analysis. No orthobiologic applications (i.e. bone stimulators or artificial/autologous graft) will be used. If it is known to the surgeon that the patient will require orthobiologic applications, the patient is not eligible for enrollment in this study. Of note, orthobiologic applications such as bone stimulators or bone graft are not traditionally used and are considered unnecessary for this bunionectomy procedure. The remaining medial bony shelf is removed and soft tissue rebalancing is performed as needed. A medial capsulorrhaphy is performed. The remaining capsule and soft tissue is sutured closed. The skin closure is based on surgeon preference, but is traditionally a running subcuticular closure using 4-0 monocryl suture. A soft, compressive, sterile dressing will then be applied and the tourniquet is then released.

**The surgical technique described above, the surgical dressing, and the post-operative care are all considered standard of care for this procedure. The only study specific procedures include telephone calls, study drug, patient diaries, and questionnaires (which will be described in subsequent sections).**

#### **A.4. Screening, Enrollment, and Post-operative Course**

##### *a. Screening, Informed Consent, and Randomization*

All subjects will be treated pre-operatively by his/her surgeon. Once the surgeon determines the patient will require a Kalish bunionectomy, he/she will review the patient's medical record to determine if the patient meets the study inclusion/exclusion criteria. If the investigator/surgeon determines that the patient meets study criteria, he/she will discuss the clinical trial with the patient. If the patient expresses interest in participating in the clinical trial, the investigator/surgeon and/or research fellow will complete a standard screening form to determine the patient's eligibility. All eligible patients will be given a copy of the informed consent form for review. A screening log will be maintained. If the patient has additional questions, he/she will be given the principal investigator's and research fellow's contact information.

On the day of the surgery (*Day 0*), the informed consent will be reviewed again with the patient by one of the investigators. If the patient decides he/she would like to enroll in this study, they will sign the informed consent form, and will be randomized in the pre-operative holding area to either ketorolac or placebo. The patient and surgeon will be blinded to which study drug he/she was randomized to. Baseline information will be recorded including baseline pain scores. Pain will be measured by both unidimensional and multidimensional instruments. This will include the McGill Pain Questionnaire-Short Form (MPQ-SF) and the visual analog scale (VAS). The VAS will be 10 cm in length with the end anchors, "no pain" and "worse possible pain".

##### *b. Immediate Post-operative:*

The following post-operative instructions detail the typical post-operative course given for this procedure. The only changes include the addition of the study drug dispensed by research pharmacy, the use of a study diary, a telephone interview two days post-operatively, and counting of remaining pills and study compliance. **The prescribed pain medication, dressings, surgical incision management, frequency of radiographs, weight bearing status, progression to activities, and**

**frequency of clinic visits are all standard of care and do not change as a result of this study.**

The surgeon may deviate if he/she feels it is necessary for a particular patient or if concomitant procedures necessitate a deviation. Any deviations will be recorded and accounted for in the analysis. We do not anticipate any significant protocol deviations. Immediate anteroposterior and lateral radiographs will be taken post-operatively. The patient will be placed in a sterile soft post-operative dressing. Research pharmacy will dispense the study medication (oral ketorolac or placebo) and standardized prescriptions will be given for opioid pain medication. Standard post-operative instructions will be given to all patients. This includes instructions for icing and elevating the foot, as well as medication instructions. Patients will be allowed to partial weight bear in a post-operative shoe with crutches due to the inherent stability of the osteotomy, given that rigid internal fixation is provided as detailed in the surgical technique. Patients will be given a study diary with instructions on how to properly record information. The post-operative care described here is considered standard of care for this procedure (except for the study drug and study diary) and not related to the study.

*c. Day Two:* Patients will be contacted by telephone two days (48 hours,  $\pm 4$  hours after the surgical procedure) by a dedicated research fellow trained in survey administration between the hours of 8am and 6pm. This person has no involvement with the surgical procedure and is blinded to the patient's randomization status. This will allow enough time for the affects of anesthesia to subside, 48 hours ( $\pm 4$  hours) following his/her surgery. This will also be well within the five day window in which the patient will be taking ketorolac post-operatively.

Pain will be measured by both unidimensional and multidimensional instruments. The McGill Pain Questionnaire – Short Form (MPQ-SF), Visual Analog Scale (VAS), pain medication related information, and study protocol compliance information will be collected at this time. The research fellow will instruct patients on how to fill out the visual analog scale (VAS) in the study diary. The VAS will be pre-printed in a diary that is given to the patient post-operatively. The VAS will have the end anchors, “no pain” and “worst possible pain”. If patient compliance with the VAS is greater than 95%, then the VAS will be used for the primary analysis. As a back-up, the MPQ-SF will be utilized as the primary analysis.

*d. Week One:* Patients will be evaluated in the clinic by his/her surgeon and re-banded. Patient diaries will be collected, post-operative medications will be counted, and study compliance will be verified.

*e. Week Two:* Sutures will be removed if appropriate and the patient may begin to get the surgical site wet. A soft bunion splint will be given to maintain soft tissue correction and is worn with the post-operative shoe for one more week. Range-of-motion exercises will be initiated and patients can be weight bearing as tolerated.

*f. Weeks Three through Five:* Anteroposterior and lateral foot radiographs will be taken at week three  $\pm$  one week. If the surgeon determines there is satisfactory healing, the patient will be transitioned to a supportive soft-soled shoe to initiate a propulsive gait. Range-of-motion exercises will be continued. The soft removable bunion splint is worn at bedtime for another 1-2 weeks.

*g. Week Six  $\pm 1$  week:* Weight bearing anteroposterior and lateral foot radiographs will be taken and the patient will be clinically assessed. If there is satisfactory healing, as determined by the surgeon, the patient can transition to normal activities. High impact activities, such as running or



jumping, will be avoided until the eighth week following surgery. Physical therapy will only be initiated if the surgeon determines its necessity. Indications for physical therapy may include a continued stiff joint or chronic edema.

*h. Week Twelve and Subsequent Visits:* Weight bearing anteroposterior and lateral foot radiographs will be taken and the patient will be clinically assessed at week twelve  $\pm$ 1 week. If there is complete osseous union on radiographs, the patient will have completed the study. If there is incomplete osseous union on radiographs, the patient will continue to be followed by his/her surgeon. The timing and frequency of these subsequent visits will be determined by the patient's surgeon.

If there is incomplete osseous union after twelve weeks, the patient will be classified as a delayed union. If there is incomplete osseous union after six months, the patient will be classified as a nonunion.

**The post-operative care described here is considered standard of care for this procedure (except for the study drug, telephone call, study diary, and questionnaires) and not related to the study.**

#### **A.5. Exposures and their measurements (ketorolac versus placebo)**

All patients will have a Kalish bunionectomy performed, fixated by two 3.0 mm cannulated partially threaded screws. Patients will follow the post-operative course as outlined above. Patients will be randomized in the pre-operative holding area to either receiving ketorolac or placebo. If randomized to ketorolac, the patient will receive one 30 mg IV dose while in the operating room under anesthesia by the anesthesiologist. If not randomized to ketorolac, the patient will receive one intra-operative 30 mg IV dose of placebo by the anesthesiologist. Patients will be given the study drug (either ketorolac or placebo capsules) after the procedure. This will be dispersed from the research pharmacy department following hospital protocols. If randomized to ketorolac, the patient will take one 10 mg capsule every eight hours, beginning approximately eight hours after the surgical procedure for a total of five days (15 capsules). If randomized to placebo, the patient will take a placebo capsule every eight hours, beginning eight hours after the surgical procedure, for a total of five days (15 capsules).

#### **A.6. Randomization and Blinding**

Eligible patients will be randomized in the pre-operative holding area to either ketorolac or placebo by stratified permuted block randomization. Stratification will be by number of forefoot procedures (isolated Kalish bunionectomy versus Kalish bunionectomy plus additional forefoot procedures) and by unilateral versus bilateral (total of four possible strata: 1. Unilateral + Isolated Kalish Bunionectomy; 2. Unilateral + Kalish Bunionectomy with additional forefoot procedures; 3. Bilateral + Isolated Kalish Bunionectomy on one side; 3. Bilateral + Kalish Bunionectomy with any additional forefoot procedures. Any correlated cases will be accounted for in the analysis and are not common at this institution (but will be stratified in the event they do occur to help ensure balance between the study groups).

Study group allocation will be controlled by research pharmacy with sequentially numbered opaque sealed envelopes. This communication will occur entirely between the surgeon and research pharmacy. Allocation of ketorolac or placebo will be recorded on a "Randomization/Treatment" log that will be stored in a secure location with both opened and unopened randomization envelopes.



Access to this secure location will be controlled and locked. A coded master list will be kept in a locked and secured cabinet.

Patients, surgeons, anesthesiologists, and any assessors will be blinded. Only research pharmacy will not be blinded. Both ketorolac and placebo capsules and bottles and intra-venous preparations will appear exactly the same and will be prepared by research pharmacy. Assessors will be collecting data on post-operative pain and radiographic unions and will not be made aware of the patient's randomization results. In the event of an emergency or where the subject safety may be at risk, research pharmacy will unblind any necessary individuals to properly care for patients. In this event, the details of revealing the assigned study drug must be recorded in the subject's source documents.

#### **A.7. Study Endpoints**

The study will be concluded once each patient achieves radiographic union at 12 weeks (please refer to grading scale in the statistical consideration section) or up to six months, whichever comes first. If a patient experiences a serious adverse event, requiring them to discontinue the study medication, they will be immediately withdrawn from the study, treated appropriately, and reported.

### **B. Statistical Considerations**

#### **a. Sample Size Justification:**

In performing the required sample size calculations, the authors assumed that potential cluster effects may be evident as a function of the individual surgeon. Because of this likelihood of cluster effects, we estimate the power of the study for change in post-operative pain that assumes an intra-class correlation (ICC) of at least 0.08 to inflate sample size estimates. This assumes 80% power to detect differences between groups with a 0.05 two-sided significance. Previous literature reports that in comparisons of opioid alone versus ketorolac with opioid the mean difference was observed to be 1.8 on the VAS (16). The widely accepted minimum clinically significant pain relief has been reported to be 1.3 (17). Detection of a 1.3 absolute difference in change in pain relief between groups requires 40 patients per group; detection of a 1.8 difference requires 20 patients per group consisting of eight and four (surgeons) respectively, assuming clusters of 10 subjects each. These calculations use an extremely high ICC which maximizes its accuracy. Because of the unknown ICC influence, a sensitivity analysis was performed assuming a non-contributory ICC of 0.08 which required a total sample size of 20 subjects per arm using the smallest clinically significant difference to detect.

Based on these calculations the largest sample required is 80 subjects. In order to preserve statistical power in the face of drop-outs and patient contact difficulties, the total sample size will be inflated by 10% such that the final projected sample size will be 88 subjects, or 44 per arm.

The next consideration for study design is the sample size calculations for delayed and nonunion in each group. Because earlier calculations have already incorporated ICC assumptions, the previous approach is still considered appropriate. Again drawing from higher level studies, the difference to detect has been determined to be 20.5% between groups (38). Using the same criteria from the previous calculations, an 80% power to detect differences between groups with a 0.05 two-sided significance will require a total sample size of 76, or 38 subjects per arm. If the ICC were to be changed to 0.01 detection of a 20.5% difference requires 40 patients per group with five clusters of sixteen patients for the total of 80 subjects. Given the ICC assumptions of the VAS calculations the authors have already attempted to incorporate a highly conservative sample calculation and included a 10% inflation for drop-outs.

**Thus, the previously noted 88 total sample size (44 patients per treatment arm) was estimated to**

**be adequate to achieve study aims and goals.**

**b. Data Analysis**

**Outcomes and their Measurements**

*a. Primary Outcome*

All analyses will be calculated using Statistical Analysis Software (SAS, Worldwide Headquarters, Cary, NC) and will be based on the **intention-to-treat principle**.

The primary outcome of interest is pain measured on the second post-operative day, 48 hours ( $\pm 4$  hours) following surgery. This will allow the effects of anesthesia to subside following surgery. This will be well within the five day window in which the patient will be taking ketorolac post-operatively.

Pain will be measured by both unidimensional and multidimensional instruments. A blinded trained research fellow will contact patients by telephone and will administer the McGill Pain Questionnaire-Short Form (MPQ-SF) and instruct patients to fill out the visual analog scale (VAS). This will occur 48 hours ( $\pm 4$  hours) post-operatively. The VAS will be pre-printed in a diary that is given to the patient post-operatively. The VAS will be 10 cm in length with the end anchors, "no pain" and "worst pain possible". If patient compliance with the VAS is greater than 95%, then the VAS will be used for the primary analysis. As a back-up, the MPQ-SF will be utilized as the primary analysis. Regardless, sensitivity analyses will be conducted to verify the robustness of the results. The research fellow will also obtain the patient's post-operative pain medication consumption (including timing and dosages) and verbally confirm study protocol compliance during this telephone interview (Please refer to the variables collected section for full details; A telephone script is also included in this IRB application). Regression will be utilized to control for measured confounders, including timing of the telephone interview and last dose of post-operative pain medication. Standard regression model rules will be applied and a p-value  $\leq 0.05$  will be considered statistically significant in the final regression model.

The patient diaries with the VAS will be collected during the first post-operative visit (one week). Patients will be asked to bring all surgery related medications and bottles to this post-operative appointment. The research fellow will again obtain the patient's post-operative pain medication consumption (including timing and dosages) by counting pills and verbally confirm study protocol compliance (Please refer to the variables collected section for full details).

Whether a difference in delayed unions at twelve weeks exists between the two groups will also be assessed. Radiographic union for each patient will be assessed by both a blinded, board-certified radiologist and two blinded board-certified podiatric surgeons. Agreement between these three experts will be assessed with a kappa score and the mean result will be used for primary analysis. Delayed and non-union rates will be compared between the two groups. A previously documented scoring system found to have both high inter- and intra-observer reliability in a series of tibial fractures reduced surgically will be utilized for this assessment. This scoring system grades each fracture according to four characteristics: 1. Rating of fracture healing, 2. Callus morphology, 3. Number of cortices visible or obliterated. 4. Number of cortices bridged (41). The modification utilized for this study will be as follows:

- ❖ **Grade 1:** Homogenous bone structure with complete obliteration of fusion site
- ❖ **Grade 2:** Massive bone trabeculae crossing fusion site, 3-4 cortices are bridged with fusion site barely discernable
- ❖ **Grade 3:** Apparent bone trabeculae crossing fusion site, 2-3 cortices are bridged with fusion site discernable
- ❖ **Grade 4:** Trace bone trabeculae crossing fusion site, 1-2 cortices are bridged with distinct visible joint space

- ❖ **Grade 5:** No bone trabeculae crossing fusion site, 0 cortices are bridged with complete visible joint space

A delayed-union will be defined as a grade 4 or 5 in any patient over twelve weeks. A nonunion will be defined as a grade 4 or 5 in any patient over six months. Analysis will include logistic regression for these binary endpoints. Odds ratios and 95% confidence intervals will be calculated between groups (delayed and/or non-union: yes/no). A 2-sided p value of  $\leq 0.05$  will be considered statistically significant.

#### *b. Secondary Outcomes*

The proportion of rescue narcotics will be compared between the ketorolac and placebo groups. Narcotics will be converted to standard morphine equivalents for statistical comparison.

On day two, the research fellow will also ask patient's his/her Global Evaluation of Study Medication by telephone. The patient will be asked, "How would you rate the study medication you received to delay pain". The choices will be on a four point scale: 1=poor; 2=fair; 3=good; 4=excellent.

Adverse events will be obtained from a standard form included in the patient's study diary. The proportion of adverse events will be compared between the ketorolac and placebo groups.

Time to regular shoe gear will be compared between the two groups. This information will be assessed during the post-operative visits and recorded within the secure BIDMC online medical record for each patient. Level of post-operative activity will also be evaluated with the help of the functional recovery index. This is a validated instrument for post-operative patients which includes three main domains: 1. Pain and social activity; 2. Lower limb activity; 3. General physical activity.

Summary statistics will be analyzed and reported. Continuous data will be analyzed with a 2-sided student's t-test if normally distributed or a Wilcoxon Rank Sum test if it cannot be justified through the Central Limit Theorem. From this data, confidence limits will be obtained and a 2-sided p value of  $\leq 0.05$  from the Fisher Exact Test will be considered statistically significant. If there are significant confounders identified, multivariate regression or stratification may be required and utilized if necessary. Binary data points will be compared by chi square analysis. From this, 95% confidence intervals will be obtained as well as a p-value from the Fisher Exact Test. A compliers-only analysis will also be secondarily performed if necessary, with the notion that this part of the study may have confounders and will not be part of the randomized comparison. Table 1 of the study will detail subject ages, gender, comorbidities, and other baseline study demographics.

#### **Missing Data**

Given that the first outcome measure occurs within two days and the second outcome occurs in twelve weeks of study enrollment, we do not anticipate that missing data will be a large concern. Protocol deviations will be recorded and reported but the primary analysis will be an **intent-to-treat analysis**. For outcomes requiring a longer follow-up duration, any patients who are lost, move or expire will be counted as treatment failures. Patients will be generally healthy as this is a population undergoing elective bunionectomy surgery. In addition, information will be collected regarding patient contact information to help prevent loss of patients. Patients that miss a follow-up appointment will have a set mechanism in-place in order to contact the patients. All available contact information

including the patient's residential and work address, work, home and cellular phone number as well as contact information of the next of kin and closest friend will be obtained for each patient. Permission to contact these people as necessary will be obtained. The short follow-up period will also improve success in these measures. Finally, there is a built in 10% increase in patient sample size if the above safety measures still fail.

Although we do not anticipate significant missing data problems, any concerns will be dealt with sensitivity analyses to determine their impact.

### **Other Variables of Interest and Their Measurements**

Because this is a randomized trial, confounders should be equally distributed between the two treatment groups. All variables will be analyzed to check if there are any differences between the two groups.

There will be many variables collected for this study. These variables include the pain score evaluations, ages, genders, patient related contact information, comorbidities, tobacco use, medications, allergies, BMIs, laboratory results, all anesthesia medications used, number of millimeters the capital fragment was transposed, fixation specifics for the bunionectomies, intra-operative complications, tourniquet time, attending of record, attending experience, pain control given in post-anesthesia holding area, pain medication taken post-operatively, pill counting and mechanisms to assess patient compliance post-operatively, timing of the telephone interview and last dose of post-operative pain medication, post-operative protocol deviations, and whether or not physical therapy was used. The study and analysis will take place and be stored at Beth Israel Deaconess Medical Center. Follow-up visits may also occur at Beth Israel Deaconess Medical Center satellite clinics for patient convenience.

## **C. Subject Selection**

### **Assembly of subjects**

All patients undergoing a first metatarsal Kalish osteotomy for bunion correction who meet study inclusion and exclusion criteria will be invited to participate in this study.

### **Inclusion Criteria:**

- Hallux abductus with bunion deformity
- Adult patients as defined by  $\geq 18$  years old and  $\leq 80$  years old
- Subject has adequate perfusion, verified by the surgeon, which is defined by palpable pedal pulses
- Subject has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board, and provided HIPAA (or other applicable privacy regulation) authorization prior to any participation in the study
- Subject agrees not to take any new medications, dietary supplements, or alternative therapies during the study period (approximately 12 weeks)
- Subject is interested in participating in the study and willing to comply with the study protocol
- Patient has pain related to a bunion deformity but pain-free metatarsalphalangeal joint (MTPJ) range of motion that is not functionally adapted
- Adequate bone density to withstand a Kalish bunionectomy procedure
- No frontal plane hallux deformity
- Minimal abnormality of the PASA

- Normal to minimally malaligned sagittal plane position of the first metatarsal
- Failure of conservative treatment
- General Pre-operative Radiographic Angle Criteria†
  - 10-15<sup>0</sup> IMA in rectus feet\*
  - 20-25<sup>0</sup> TAA in adducted feet\*
  - 15-20<sup>0</sup> IMA in rectus feet if wide metatarsal head width
  - 25-30<sup>0</sup> TAA in adducted feet if wide metatarsal head width

*IMA=intermetatarsal angle; TAA=total adductus angle*  
\*If the pre-operative IMA is <15<sup>0</sup>, only the IMA will be used pre-operatively. For IMA ≥15, the total adductus angle will be used  
†These are general guidelines and the width of the metatarsal as well as the presence of positional, structural, or combined first ray deformity may also influence procedure selection (51-52).

Exclusion Criteria:

- Patients with a contraindication for ketorolac will be excluded from the study. This includes patients with:
  - a history of an allergic-type reaction in response to exposure to aspirin, phenylacetic acid derivatives, or other NSAIDs
  - hypersensitivity to ketorolac tromethamine, or to any product component
  - any known bleeding risk or bleeding disorder, suspected or confirmed
  - history of or active cerebrovascular bleeding, suspected or confirmed
  - concomitant aspirin or NSAID use where the patient may not be advised to discontinue the medication during the study
  - concomitant pentoxifylline use
  - concomitant probenecid use
  - coronary artery bypass graft (CABG) surgery within one year of the procedure
  - any history of gastrointestinal bleeding/perforation, gastrointestinal ulcer, severe peptic ulcer disease, or severe inflammatory bowel disease
  - hemorrhagic diathesis, suspected or confirmed
  - incomplete intraoperative hemostasis
  - pre-operative serum creatinine > 1.5 ml/dL or blood urea nitrogen level > 22 mg/dL
  - any history of renal impairment or risk of renal failure due to volume depletion
- Patients with a known allergy, contraindication and/or intolerance for oxycodone 5mg – acetaminophen 325 mg will be excluded from the study.
- Patients with a known allergy, contraindication, and/or intolerance for the local anesthetic (bupivacaine) or any of the standardized intra-operative opioids and anti-emetics administered by the anesthesiologist
- Patients with a history of fibromyalgia or opioid abuse
- History of chronic regional pain syndrome or diagnosis of any chronic pain syndrome, patients requiring routine methadone or other opioids
- Neuropathy or radiculopathy
- Subject has alcohol or substance abuse, dementia, brain metastases, or other cognitive disorders that may interfere with pain assessment and the post-operative course outlined by the surgeon



- Patients with a contraindication for elective surgery will be excluded and includes:
  - American Society of Anesthesiologists (ASA) Physical Status class four or higher
  - women who are pregnant, planning on becoming pregnant, or breast feeding
  - presence of active local or systemic infection
  - subject has a myocardial infarction in the last twelve months
  
- Patients who are not candidates for a Kalish bunionectomy due to the preoperative deformity as well as other study exclusions are:
  - Absent pedal pulses or  $ABI \leq 0.9$  and  $\geq 1.2$
  - Concomitant midfoot and rearfoot procedures
  - Moderate to high abnormal PASA angles
  - Significant sagittal plane first metatarsal deformity
  - Moderate to severe osteoporosis as evaluated by preoperative radiographs and/or bone mineral density tests
  - Revision cases
  - History of previous infections, radiation treatment, or current infection related to the surgical site
  - History of previous trauma of the first metatarsal or first ray
  - Subject has known immunosuppression (HIV, recent chemotherapy, organ transplant)
  - Patients taking systemic steroid (patients taking less than 5 mg of prednisone, inhaled steroids for asthma or chronic obstructive pulmonary disease, topical or optical steroids will not be excluded)
  - Subject has active malignancy, excluding cutaneous malignancies except melanoma

### **Pregnancy**

Elective bunion surgery will not be performed if the patient is pregnant or planning on becoming pregnant during this study. It is standard practice to obtain urine testing in all women of child bearing potential prior to elective surgery to ensure she is not pregnant. Furthermore, if the subject is a woman capable of becoming pregnant, she must agree to use adequate birth control. For the purpose of this study, use of adequate birth control includes one of the following:

1. oral hormonal contraceptives;
2. implanted hormonal contraceptives (intramuscular progesterone injections);
3. diaphragm with spermicide;
4. condoms;
5. Intra-uterine device;
6. abstinence.

In the event a patient believes she may have become pregnant while participating in this study, she must inform the study investigator immediately and take a pregnancy test. If it is determined that she is pregnant, she must withdraw from the study immediately.

If the subject is a man capable of fathering children, he must use adequate contraception while participating in this study. For the purposes of this study, adequate birth control means;

1. use of a condom or
2. his partner must use an approved method of birth control as listed above or his partner has experienced menopause or has had a hysterectomy or
3. abstinence

#### **B4. POSSIBLE BENEFITS**

No benefit is guaranteed to the patient for the participation in this study.

The primary objectives of the Kalish procedure are to reduce pain and improve function. All surgical procedures, even if they are elective out-patient surgeries, are associated with post-operative pain. As care providers, surgeons seek to achieve these surgical objectives while minimizing the pain that their patients experience. COX-2 inhibitors were considered to be an alternative to traditional NSAIDs but their use have suffered substantial drop off given concerns over potentially life-threatening adverse events. Ketorolac is a nonselective NSAID, inexpensive and widely available. Prior literature demonstrates that NSAID use in the post-operative period may reduce overall pain experienced and the frequency of opioid use. This represents a possible benefit to patients. Many surgeons already use ketorolac as described in this protocol, while others have concerns about delay in bone healing. The proposed study would provide evidence that has the potential to impact the standard of care throughout the United States in podiatric and orthopedic communities.

For the medical community as a whole, regardless of the outcome, this study and subsequent publications will represent the first randomized control trial on this topic. The study design will test the hypothesis such that the results will provide strong evidence that will advance either the supportive or detracting arguments.

#### **B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO**

There is a potential risk that patients randomized to the ketorolac group may experience adverse events. Our inclusion/exclusion criteria were carefully designed to prevent enrollment of study subjects at risk for developing adverse events related to ketorolac. Only patients between the ages of 18 – 65, with an ASA less than four will be enrolled. In addition, patients with coagulation disorders, history of gastrointestinal bleeding or ulcer, renal failure (as defined by creatinine >1.5 ml/dL, utilizing other studies as reference), or blood urea nitrogen levels >22 mg/dL will be excluded from the study (please refer to inclusion/exclusion criteria for full details). This will eliminate subjects at the greatest risk for developing ketorolac related adverse events. Finally, we are utilizing a low recommended dose of ketorolac with a total duration of five days to also minimize potential side effects. If however, a patient does experience an adverse event believed to be related to ketorolac, they will be instructed to immediately contact his/her surgeon and discontinue the medication. All adverse events will be reported, following all of our institution's IRB guidelines and protocols.

There will be a mechanism in place in the event there is an emergency to unblind any necessary individuals. All patients will be given the on-call podiatry pager number and instructed to utilize this number if they experience any adverse events or concerns. One of the podiatry investigators will be on-call and available to study patients at all times. The surgeon investigator will have the capability of determining whether or not the patient should discontinue the study and can unblind anyone he/she deems necessary by contacting research pharmacy should an emergency or adverse event occur.

Most of the post-operative course is considered standard of care. It will be explained in advance to patients that they will be asked to fill out a study diary, be contacted approximately two days following the surgery, and asked to remember to bring in the diary and all pain medication during his/her first post-operative visit. The duration of the telephone call two days post-operatively is estimated to take approximately 20 minutes based upon adding up the reported time of the individual questionnaires in previous studies (54,55). Although this will consume a portion of the patient's time, the patient will be made aware of the telephone call and duration in advance and has the opportunity to decline participating in this study. This also gives the patient the opportunity to report any problems he/she may be experiencing post-operatively.



There will also be procedures in place for protecting patient confidentiality. All data (CRFs, source documents, patient's questionnaire, patient diaries) will be stored in locked cabinets at Dr. Emily Cook's office. Only study personal will have access to these cabinets. Clinic notes and radiographs will be entered into the internal BIDMC online medical record (OMR) within the BIDMC secure server, behind the BIDMC firewall. Only personnel approved by our institution's IRB will be allowed to access this information. Research personnel in our group who have a need to access patient information have been trained to be highly sensitive to patients and their protected health information. In addition, all patient/subject protected health information is stripped from radiographic images and other data when they are moved to other computers for data processing.

The benefits of this treatment protocol to the individual and to the population at large clearly outweigh the risks to both groups.

## **B6. RECRUITMENT AND CONSENT PROCEDURES**

### **Recruitment**

Previous long-term large clinical trials, through several NIH grants, have been conducted at our center. We will have access to a dedicated clinical research room as well as experienced and qualified research assistants who have successfully participated in numerous clinical trials. In addition, our facility hosts a dedicated two-year podiatric reconstructive and research fellowship and a podiatric medicine and surgery-36 residency.

Patients will be recruited from a large tertiary care institution which has one major primary foot and ankle clinic with satellite podiatry offices scattered throughout a metropolitan area. The demographics of the satellite patients are similar to those seen at the primary center for elective cases including bunionectomies. There are over 12,900 annual visits at the primary clinic and over 10,000 annual visits at the satellite clinics.

Surgical cases at our institution were reviewed for volume over the past two years. Adequate numbers of surgical cases were identified in both financial years 2007 and 2008 with 6 participating surgeons. An additional two surgeons have joined the staff in 2009 and volume is expected to either remain stable or increase. All eight surgeons are either board certified or board eligible by the American Board of Podiatric Surgery in both Foot Surgery and Reconstructive Rearfoot and Ankle Surgery. All are well versed in the indications and technique associated with the Kalish bunionectomy procedure. Please note that the power calculation also takes into account the estimated differences between surgeons by cluster analysis. Final analysis will also assess for differences between surgeons and surgeon experience and control for this by regression analysis if necessary.

### **Consent**

#### **Screening**

A waiver of consent is being requested in order to screen patients for possible study enrollment. All subjects will be treated pre-operatively by his/her surgeon and we are recruiting from our own patients only. Once the surgeon determines the patient will require a Kalish bunionectomy, he/she will review the patient's medical record to determine if the patient meets the study inclusion/exclusion criteria. If the investigator/surgeon determines that the patient meets study criteria, he/she will discuss the clinical trial with the patient. The investigator will fully explain the purpose of this study to the patient. The discussion will include the potential risks and complications, time commitment, and the alternative treatments. In addition to the oral explanation of the project, the investigator will be available to answer all questions that the patient may have after reading the informed consent document. If the patient expresses interest in participating in the clinical trial, the surgeon or research fellow will complete a standard screening form to determine the patient's eligibility. All eligible patients will be given a copy of

the informed consent form for review. A screening log will be maintained. The patient will be given the principal investigator's and research fellow's (who is a co-investigator in this study) contact information should he/she have additional questions.

#### **Enrollment**

On the day of the surgery (Day 0), the informed consent will be reviewed again with the patient by one of the study investigators. The Investigator will be responsible for obtaining written informed consent from each patient. If the patient decides to enroll into the study, the patient will sign the informed consent in the pre-operative holding area prior to his/her surgery and prior to receiving any anesthesia-related medications. Once the patient has signed the informed consent form, he/she will be randomized in the pre-operative holding area and enrolled into the study.

#### **Subject Protection**

Participation in this study is completely voluntary. The patient will have the right to decide not to take part in this study. If patients choose to participate, they have the right to leave the study at any time. If the patient decides not to participate in the study or decides to leave the study early, his/her decision will not affect their relationship with their surgeon. We do not anticipate enrolling subjects who would be more vulnerable than the general population. The investigators will not pressure patients in any way to participate in this study.

### **B7. STUDY LOCATION**

#### **Privacy**

All screenings, surgeries, and follow-up evaluations will take place within BIDMC. Patient appointments may include the BIDMC satellite clinics as well as the Boston campus, which are all HIPPA compliant.

- Beth Israel Deaconess HealthCare Chelsea, 1000 Broadway, Chelsea, MA
- Beth Israel Deaconess Medical Care Center Lexington, 482 Bedford St. Lexington, MA
- Beth Israel Deaconess Medical Center: Bowdoin Street Health Center  
230 Bowdoin St. Dorchester, MA

Telephone phone calls from the trained research fellow (who is a co-investigator in this study) will take place within Dr. Emily Cook's BIDMC-Boston office. Patients will be given advanced notice that he/she will be called two days after his/her surgery so that they can properly plan where they would like to be during this telephone conversation. Study subjects will inform an investigator of the telephone number they would like for us to use during this telephone call. A back-up telephone number will be requested as well in the event the research fellow is unable to reach the patient with the first telephone number given. Only the minimum amount of data is being collected that is necessary to accomplish the research purposes.

### **B8. DATA SECURITY**

All data (CRFs, source documents, patient's questionnaire, patient diaries) will be stored in locked cabinets at Dr. Emily Cook's office. Only study personal will have access to these cabinets. Clinic notes and radiographs will be entered into the internal BIDMC online medical record (OMR) within the BIDMC secure server, behind the BIDMC firewall. Only personnel approved by our institution's IRB will be allowed to access this information. Research personnel in our group who have a need to access patient information have been trained to be highly sensitive to patients and their protected health information. In addition, all patient/subject protected health information is stripped from radiographic images and other data when they are moved to other computers for data processing.

## B9 Multi-Site Studies

Is the BIDMC the coordinating site or is the BIDMC PI the lead investigator of the multi-site study?

Yes  No

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