A. INVESTIGATIONAL PLAN

Purpose

Fractures of long bones constitute the majority of emergency operating room procedures in most trauma centers. Of these long bone injuries, tibial fractures are the most common. The National Center for Health Statistics reports an annual incidence of 492,000 fractures of the tibia and fibula per year in the United States. Patients with tibial fractures remain in the hospital for a total of 569,000 hospital days and incur 825,000 physician visits per year in the United States. Delayed fracture healing is a common complication associated with high-energy tibia fractures. Open tibia fractures with bone loss rarely unite without a secondary intervention. Delayed bone grafting of the defect is commonly used to provide stimulus for healing. The use of an autogenous iliac crest bone graft (ICBG) has remained the gold standard in the treatment of tibial non-unions with a bone defect. However, there are significant limitations to autogenous bone grafting, including the increased risk of infection from a second surgical incision and pain associated with the bone graft harvest site, which may range from 1-5 days to more than a year. Additional risks include iatrogenic fracture and damage to neurovascular structures. Also, not all patients are suitable donors. Relative contraindications to ICBGs include previous iliac crest harvesting; poor bone quality secondary to underlying disease, smoking or medications that affect the quality of bone; and advanced patient age. Finally, there is a finite amount of bone that may be obtained from the ilium, and it may not be adequate in all donors to address critical size defects. Recent technological advances with the advent of recombinant bone morphogenetic proteins emerging as a viable bone graft substitute may offer a viable alternative for patients.

The purpose of our study is to evaluate the use of one such recombinant protein in patients at a high risk for nonunion. We will evaluate open tibial shaft fractures treated with an intramedullary nail and a circumferential bone defect of at least one centimeter in length compromising at least 50% of the circumference of the bone. Patients with critical sized defects who undergo a planned, secondary grafting or whose fractures fail to demonstrate progression towards union over three consecutive months of radiographic and clinical evaluation will be included. Patients will be randomized to the use of recombinant human bone morphogenetic protein 2 (RhBMP-2) or standard ICBG to stimulate healing. The ability to restore skeletal integrity without the morbidity associated with bone graft harvesting would represent a major advantage for the patient. As a secondary evaluation, given that rhBMP-2 has been associated with decreased infections when used in open tibia fractures, we will also determine if patients with these severe fractures have a decreased infection rate with the use of rhBMP-2/ACS relative to the control group. In addition, the overall economic impact of the 2 treatment groups will be evaluated with a cost effectiveness evaluation.

Research Question:

Primary:
What is the relative effect of rhBMP-2/ACS versus autogenous ICBG on rates of union in patients with critical size defects following tibial shaft fractures?

Null hypothesis: rhBMP-2/ACS has the same union rate when used in critical-sized defects as does ICBG.

Secondary:
What is the relative effect of rhBMP-2 versus autogenous ICBG on infection rates in patients with nonunion or critical size defects following tibial shaft fractures?

Null hypothesis #2: The infection rate in open tibias with critical-sized defects treated with rhBMP-2 and autogenous ICBG are the same.

What is the economic impact of the use of RhBMP 2 for tibial fractures with critical sized defects?

Null hypothesis #3: There will be no difference in the economic cost of the treatment of critical sized defects using the RhBMP-2 versus iliac crest bone graft.

This investigation is a prospective, stratified, parallel, randomized, blinded multicenter trial to evaluate the use of rhBMP-2/ACS in 25 patients versus a control group of 25 patients who have tibial fractures with critical size defects. A committee of orthopaedic surgeons will independently adjudicate our primary outcome, fracture healing at 12 months. Participating centers are part of the Major Extremity Research Consortium (METRC) and have experience with performing randomized clinical trials. Approval by each center's institutional review board will be obtained prior to commencing the study and we will follow the research guidelines set forth by each site.

Protocol

The patients who provide informed consent will be randomized to one of two treatment groups: Patients in the control group (C) will not receive the rhBMP-2, but instead will be treated with an autogenous iliac crest bone graft. Patients in the treatment group (T) will receive 1.50 mg/ml -12 mg of rhBMP-2 soaked on an absorbable collagen sponge (rhBMP-2/ACS) as an adjuvant to a freeze-dried cancellous allograft. Each patient will be separately randomized via a computer-generated number at the Data Control Center. The grafting material for both groups will be surgically implanted on a delayed basis. For our study, patients will be bone grafted between six and sixteen weeks after the initial injury. In an acute fracture setting, autogenous bone graft is not indicated for at least the first six weeks as the factors present in the fracture hematoma and in the fracture region would lead to consumption of the autogenous bone graft. It is not appropriate for anyone to be considered for acute bone grafting in tibial shaft fractures until at least six weeks after the initial injury. Time intervals for the bone graft surgery are between six and sixteen weeks after injury with no evidence of fracture healing on the radiographs. In addition, sometimes the soft tissue injury which accompanied the tibial shaft fracture may be so extensive that even at 16 weeks it may not be an appropriate soft tissue envelope in order to operate through. We leave that to the discretion of the surgeons when it is safe for intervention to promote healing. However, if the patient's treatment plan does not include bone graft within 16

weeks of injury, the patient will not be eligible to participate. The literature supports interventions for non union be considered after 6 months from injury. This will guard against enrolling patients with "non-unions". Patients eligible for this study all had open fractures with bone defects. The soft tissue envelope needs to adequately recover from the original injury to be safe for additional surgery. Extending the window until 16 weeks permits time for adequate soft tissue recovery for the surgical procedures.

The case report form provides a space to record the size of the defect as measured from the AP and lateral x-rays. The measurement should be recorded as a total of the length, width and depth of the defect. Because an intramedullary nail is in place, the depth of the defect is to be recorded as the cortical thickness. In addition, there should be measurements made of the defect volume intra-operatively. The extent of the intra-perative defect will include area of bone loss >25% of the circumference to avoid measurement of small spikes that are clinically irrelevant. Intra-operative defect size will be recorded on case report forms.

The patients in the control group will undergo iliac crest bone graft surgery per the surgeon's usual practice. The treatment group will be managed in a similar fashion, with the rhBMP-2/ACS placed at the site of bone defect on a collagen sponge carrier per manufacturer's instructions. The patients will receive crushed cancellous allograft packed into the defect prior to an overlay of the rhBMP-2/ACS. The maximum amount of allograft chips is 60 cc to be used to fill the defect. The allograft chips will be loosely packed to fill the cortical defect flush to the cortical bone. After the allograft is implanted into the site and there is an adequate hemostasis, the RhBMP2 sponge will be applied as an overlay covering the allograft and bridging the proximal and distal tibial fragment of the defect; that is laying flat on the surface. The sponge is not to be folded, rolled or placed in any other configuration. The sponge requires no sutures to be held in place. If the patient requires more than one large pack of Infuse, they will be excluded from the study. This RhBMP2/ACS implant will be placed directly adjacent to viable muscle bed. A drain will not be used. Wound closure will commence when hemostasis is obtained. The amount of cancellous chips and brand used will be recorded on the case report form.

Medtronic Sofamer Danek markets rhBMP-2/ACS as INFUSE Bone Graft. They have agreed to provide kits of rhBMP-2 to the 25 patients randomized to the treatment group. This donation is unrestricted. Medtronic Sofamer Danek will not be a participant in the study, nor will have any access to patient or study data or any input into data analysis, results and presentations.

The patients in both groups will be evaluated at 2 weeks, 6 weeks, 12 weeks, 18 weeks, 6 months and 12 months. Outcome measures will be "union," "wound healing and infection," and "need for further intervention." Pain will be documented using the Visual Analogue Scale (VAS) at each visit. Short Form-12 (SF-12) and the Short Musculoskeletal Functional Assessment (SMFA) will be completed at 6 months and 12 months. Billing information will be obtained at the end of the 12 month study period to estimate cost of care in both treatment groups.

Consent Procedures

Written consent will be obtained during the clinic visit when bone graft surgery is scheduled. Prior to bone grafting procedure, female patients will be given a pregnancy test. Those with a positive pregnancy test will no longer be eligible and will receive standard treatment (iliac crest autograft). Patients with an active infection at the operative site, purulent drainage from the fracture or evidence of active osteomyelitis are not eligible for the study. Active infection will be defined clinically by skin changes, including redness, warmth and active drainage. Additionally, the diagnosis can be supported by laboratory values, including elevated WBC , ESR and CRP. Osteomyelitis is suspected by radiographic evidence of lytic lesions . If , at the time of surgery, the surgeon is concerned that the patient has a deep wound infection because of intra-operative findings that may include loose hardware, purulence or aninflammatory tissue reaction – the patient will be excluded from the study.

Informed consent will be obtained before any study procedures are initiated. The consent form will be reviewed in its entirety with the patient by the surgeon and research coordinator and all questions will be answered. Investigators will ask the subject questions to assure understanding before the consent for participation in the study is signed, specifically:

1. Can you explain what it means to be involved in this study?
2. What should you do if you no longer want to participate in the study?

If the patient cannot answer these questions, the patient will be deemed by the investigator to be incapable of providing informed consent secondary to a lack of mental competence; the subject will not be enrolled into the study.

Inclusion/Exculsion Criteria

Criteria For Inclusion Of Subjects:

- Patients 18-65 years old with an open tibia fracture involving diaphysis (if patient has a bilateral tibia fracture and both require a bone graft, then each will be randomized separately).
- Tibia fractures with a circumferential bone defect of at least one centimeter in length compromising at least 50% of the circumference of the bone.
- The definitive treatment of the tibia fracture must be with an intramedullary nail (may have temporary external fixation prior to IM nail placement).
- Patients whose treatment plan includes placement of a bone graft between 6 to 16 weeks after their initial injury.
- Patients who have no evidence of infection by clinical examination (defined as active infection at the operative site, purulent drainage from the fracture or evidence of active osteomyelitis at the time of bone graft).
- Patients who are independent in living and ambulation prior to injury.
- Patients who are English speaking.
- Patients who are willing to provide consent and available for follow-up for at least 12 months following definitive surgical procedure.

Criteria For Exclusion Of Subjects:

- Patients who are pregnant or lactating.
- Patients with known hypersensitivity to rhBMP-2 or bovine type I collagen.
- Patients with a history of tumor, a resected or extant tumor, an active malignancy, or patients undergoing treatment for malignancy.
- Patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).
- Patients with inadequate neurovascular status, e.g. high risk of amputation.
- Patients with compartment syndrome of the affected limb.
- Patients with immune deficiency or history of auto-immune disease,
- Patients who have undergone treatment of any other investigational therapy within the month preceding implantation or planned within the 12 months following implantation.
- Patients unable to return for required follow-up visits.
- Patients who have medical co-morbidities that preclude treatment with a general anesthetic.
- Patient who is pending incarceration or who is incarcerated.
- Patients with an active infection at the operative site defined clinically by skin changes including redness, warmth and active draining, purulent drainage from the fracture or evidence of active osteomyelitis based on radiographic evidence of lytic lesions at the time of bone grafting.
- Patient has segmental defects longer than 5cm in length as measured on AP and lateral radiographs of the injury taken after the final debridement following internal fixation
- Patient has a segmental defect longer than 6cm as measured intraoperatively after debriding .
- Patients who have segmental defects that require more than 60 cc of bone graft.
- Patients who require more than one large kit of rhBMP-2 at time of surgery.
- Patient's anticipated treatment plan also includes the use of other procedures to promote fracture healing, e.g. ultrasound, magnetic field or electrical stimulation.
- Patient's tibia fracture has been treated with additional fixation beyond the intramedullary nail, e.g. plates, wires or screws, and additional surgical fixation, e.g. fibulectomy, exchange nail and dynamization of locked nail
- Patients who have pathological fractures; a known history of Paget's disease or known history of heterotropic calcification.
- Patients with a Glasgow Coma Scale less than 15 (less than fully awake) at the time of informed consent.
- Patients with previous hardware in place that prevents placement of an intramedullary nail for treatment of the tibial shaft fracture.
- Patients with prior use of INFUSE.

If the patient is a female of child bearing potential:

- Does she have a negative pregnancy test (administered within 72 hours prior to surgery)?
- Has she agreed to use adequate contraception for a period of at least 1 year following implementation of rhBMP-2?

Number of Sites/Investigators/Patients

There will be up to a total of twenty two (22) sites enrolling patients, all of which are familiar with randomized clinical trials and are part of the Major Extremity Research Consortium (METRC). Approval by each center's institutional review board will be obtained prior to commencing the study and we will follow the research guidelines set forth by each site. A total 50 patients will be enrolled in this study. The definitive treatment of the tibia fracture in all patients must be with an intramedullary nail. The number of patients enrolled at each site will be dependant on the random nature of the admission to hospital of eligible patients. No one site will enroll more than 10 patients in this study.

The randomization scheme is a central, computerized process using a web based, distributed data collection system. A block randomization scheme with no subgroups will be used for each center participating in the trial. Blocks will use randomly permuted sizes of even numbers only, consisting of an equal number of treatments in each block. The order of the treatment assignments in each block is random. Along with treatment allocation, each patient randomized is assigned an individual study number.

Surgical Treatment

All patients will be treated with open reduction and internal fixation consisting of an intramedullary nail prior to their staged bone grafting procedure. Prior placement of a PMMA antibiotic spacer may be performed at the discretion of the surgeon to temporarily occupy the tibia fracture defect site and preserve space for the bone graft (these are to be removed prior to the bone grafting procedure).

The use of a PMMA spacers at the time of the initial injury is at the discretion of the surgeon. It will be recorded in the case report form. Antibiotic PMMA spacers may be used if there is a significant area of tissue and bone defect in a contaminated wound

Patients in the control group will receive the standard of care, cancellous autogenous bone graft harvested from the iliac crest using a standard surgical technique. Patients in the investigational treatment group will receive one INFUSE Bone Graft Large II kit (12 mg) in combination with freeze-dried cancellous allograft bone chips. Regardless of treatment assignment, the grafting material will be surgically implanted between 6 and 16 weeks after initial injury.

Autogenous Bone Graft Preparation

For the autograft group, autogenous bone graft will be harvested from the iliac crest in the standard surgical fashion. If the recipient fracture site is free of infection, we will prepare the recipient site to expose bleeding bone. The approach chosen by the surgeon will be an anterior or posterior approach depending on the position of the fracture defect and the condition of the surrounding soft tissues. The autograft will be implanted within the fracture defect and to fill the fracture defect and along the proximal and distal margin.

INFUSE Bone Graft Preparation

The INFUSE Bone Graft should be prepared according to the manufacturer's instructions listed on the product; briefly 8.4 mL of Sterile Water for Injection is mixed to reconstitute the rhBMP-2 to a concentration of 1.50 mg/mL, 8.0 mL of this rhBMP-2 solution is then uniformly distributed onto the 3" by 4" bovine collagen sponge supplied in the kit, allow the wetted collagen sponges to stand for a minimum of 15 minutes before implantation.

Bone Grafting Procedure

Up to 60 cc of bone graft (cancellous autograft bone or allograft bone) will be used to fill the tibia fracture defect. The grafting approach should be selected according to the position of the fracture and the condition of the surrounding soft tissues. Either an anterior or posterior approach is acceptable as long as the graft is placed in an area surrounded by a viable muscle mass. The proximal and distal margins of the defect site may be roughened with a burr or osteotome to expose bleeding bone. The bone graft is applied in and around the area surrounding the defect site until the defect is full. For the investigational patients, the INFUSE Bone Graft will be applied as an overlay after the defect has been first filled with cancellous allograft bone chips, the collagen sponge should bridge from proximal to distal end and cover the defect as much as possible based on the surgical opening.

Duration/Follow-up Schedule

It is anticipated that the required patients will be enrolled into this study during an 18-month period and will be followed for one year. Thus, the data collection time is anticipated to be a 2.5 year period. The patients will be evaluated at 2 weeks, 6 weeks, 12 weeks, 18 weeks, 6 months and 12 months according to the following schedule:

Follow-Up Schedule	Process	Data Collected
Enrollment	Clinical examination	Inclusion/Exclusion criteria, patient characteristics, fracture characteristics, surgical summary, VAS
2 weeks	Clinical examination, functional outcomes	Clinical follow-up data, VAS
6 weeks	Clinical examination, functional outcomes, radiographs	Clinical follow-up data, VAS
12 weeks	Clinical examination, functional outcomes, radiographs	Clinical follow-up data, VAS
18 weeks	Clinical examination, functional outcomes, radiographs	Clinical follow-up data, VAS
6 months	Clinical examination, functional outcomes, radiographs	Clinical follow-up data, VAS, SF12, SMFA
12 months	Clinical examination, functional outcomes, radiographs	Clinical follow-up data, VAS, SF12, SMFA

Measurements

Effectiveness Evaluation (x-ray, weight bearing, 2nd procedures)
Outcome measures will be "radiographic union," "clinical union", "wound healing and infection," and "need for further intervention."

Pain-will be documented using the Visual Analogue Scale (VAS) at each visit.

Short Form-12 (SF-12), Short Musculoskeletal Functional Assessment (SMFA) will be completed at 6 months and 12 months.

The **SF-12** questionnaire was developed from the Medical Outcomes Study. It is a self-administered, 12-item questionnaire that measures health-related quality of life in 8 domains. Both physical and mental summary scores can be obtained. Each domain is scored separately from 0 (lowest level) to 100 (highest level). The instrument has been extensively validated and has demonstrated good construct validity, high internal consistency, and high test-retest reliability. Our decision to use the SF-12 over other available instruments was based on its widespread use in orthopaedics, its use in previous studies evaluating fracture outcomes, and the strong evidence of validity.

The **SMFA is** a shorter version of the 101 item Musculoskeletal Function Assessment (MFA) questionnaire. The SMFA is a 46 item questionnaire consisting of the dysfunction and bother index. The dysfunction index has 34 items for assessment of patient function, while the bother index consists of 12 items designed to detect how much patients are bothered by functional items. The SMFA has been evaluated for reliability, validity and responsiveness in patient populations. We chose this scale because it is a short, validated instrument to provide us with information regarding the patient's functional status.

Safety Evaluation (complications, re-operations, adverse events)

Wound Complications

- Deep infections are defined as those that occur within one year from the procedure, involve deep soft tissue and that meet at least one of the following criteria: "purulent draining, a deep incision that spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38 degrees C), localized pain or tenderness, unless the incision is culture negative; an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathology or radiologic examination; or diagnosis of a deep incisional SSI by a surgeon or attending physician" or require operative treatment.. All treatment and interventions will be recorded.
- Superficial infections are defined as those that occur within 30 days after the operative procedure and involve only skin or subcutaneous tissue of the incision and at least one of the following: purulent drainage from the superficial incision; organisms isolated from an

aseptically obtained culture of fluid or tissue from the superficial incision; at least one of the following signs or symptoms of infection- pain or tenderness, localized swelling, redness or heat and the superficial incision is deliberately opened by surgeon unless the incision is culture=negative; or diagnosis of superficial incisional SSI by the surgeon or attending physician" and that are treated only with local antibiotics and wound care, and no operative treatment for the infection (Horan TC et al, 1992).

Swelling: Swelling will be defined as the absence of skin wrinkling.

Fracture Healing

Radiographic union will be measured by evidence of fracture healing defined by the Radiographic Union Scale in Tibial fractures (RUST) score, Clinical union will be defined by: 1. Pain free full weight bearing and/or 2. The absence of pain to palpation at the fracture site.

Clinical Success will be determined by the clinical investigators on the basis of both:

1. Radiographic evaluation will be assessed by blinded orthopaedic surgeons and will use consensus adjudication to determine union measured by the RUST score.

2. Clinical healing is defined as pain free, full unsupported weight bearing and lack of tenderness at the fracture site on palpation. The fracture will be considered to be a Clinical Success (e.g. healed) when radiographic union is confirmed and both clinical parameters listed above for healing has been met.

Economic Outcomes

An economic evaluation will also be performed including the costs of iliac crest bone graft harvest and complications from the bone graft surgery and the cost of the Rh-BMP 2 and the biologic implant used in the treatment group. Billing information from CMS forms UB04 and 1500 along with discharge abstracts will be obtained for treatment received by study participants at the pTOG study site hospital(s) and clinics at the end of the 12 month follow-up period. Billing records will not be collected for treatment received at hospitals or clinics not affiliated with the pTOG study. However, it will be important to document the types of treatment received so that costs for non-study site admissions and outpatient visits can be estimated during the final analysis. Therefore, during scheduled follow-up visits, patients will be asked about medical care received since the prior study visit. Responses as documented in the case report forms will provide a basis for estimating treatment costs.

Statistical Analyses/Data Presentation

Sample Size Justification

To address our primary objective, a comparison of healing rates between BMP and Autogenous Bone Grafts, we assume at 20% higher healing rate in BMP treated patients (Jones et al, 2006), with a baseline healing rate of 65% (with autogenous bone graft). Stipulating a study power of 80% and an alpha level=0.05, and a non-inferiority margin of 20% our study will require at least 14 patients per treatment arm. If we stipulate our non-inferiority margin to be 10%, we will require 25 patients per group. Thus, to be most conservative, our study will recruit 50 patients total (25 patients per treatment arm). We will complete an interim evaluation of results once 25 patients have been enrolled, including a power analysis.

Final Analysis

The results will be reported comparing the outcomes in the groups at each follow-up period. It is anticipated that the required patients will be entered into the investigation during an 18-month period and will be followed for one year. Thus, the data collection time will be a 2.5- year period. We believe that at that time, the results of the study will reveal whether any differences exist with this high-energy disabling fracture in terms of outcomes, union rates, times to union, soft-tissue complications and infection rates.

Data will be analyzed on an intent to treat basis (patient data included in the treatment group and stratum to which randomized). Fishers exact test will be used to compare categorical variable and the Student t test will be used for continuous variables for comparisons between the two groups.

Quality of life data will be coded and scored according to the guidelines provided with the SMFA (Coding Key Manual, Musculoskeletal Function Assessment, Injury and Arthritis Survey) and the SF-12 (Coding Manual for the SF-12 Health Survey).

Data Security and Protection Plan

All data will be collected on Case Report Forms provided to the participating sites by the Coordinating Center. The research coordinators at each site will obtain the information necessary to complete the case report forms (CRFs) from several sources including the patient's medical record, clinical evaluations and patient interviews. These forms will NOT contain the patient's name, SSN, or hospital medical record number; they will be identified only by a unique patient-specific study number.

The Site Research Coordinator will enter non-personally identifiable information into a central and secured web-based data management system being implemented for all Consortium studies, known as REDCap. This data management system has incorporated state-of-the-art features for electronic data collection and is configured in accordance with best practices for information technology and research data management

Hard copy documents containing subject data and patient identifiers (and contact information) will be stored in secure document containers (file cabinets, lockers, drawers, etc.) in accordance with standard document management practices. The data collection forms will be destroyed within five years after study completion, as will the file linking study numbers with personally identifiable information. Paper forms will be shredded and the file containing personally identifiable data at each site will be deleted from local site computers. Each site will provide the Coordinating Center a signed verification that these data have been destroyed.

All research data, in hard copy or electronic form, will be stored and managed in a secure manner following applicable federal regulations and guidelines and according to institutional policies and practices.

At all times, only listed key personnel specifically designated and authorized by the Principal Investigator shall have access to any research related documents, including electronic data. All such personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct

Risk Analysis

Risks Associated with Experimental Treatment: The use of rhBMP-2 in the staged bone grafting of a tibial shaft fractures with a bone defect is currently off-label. BMP-2 is approved for extremity trauma for open tibial shaft fractures within the first 14 days after injury. However, we are not intending to support a new indication for its use or not intending to support a significant change in advertising for the product; the route and dosing of administration and subject population is the same as currently used according to FDA approvals; the study will be conducted in compliance with IRB review and informed consent and also in compliance with the requirements concerning the promotion and sale of the drug and it does not intend to invoke the Humanitarian Device Exemption. Based on the result of animal and human studies, rhBMP-2 may help bone to heal faster than it normally would without rhBMP-2. It is possible that the subject will get the BMP-2 treatment but do less well than he/she would have done with standard care alone. Also because the treatment is relatively new, we may not yet know the side effects: something unexpected could happen.

Possible risks of rhBMP-2 (the side effects reported by 1% to 10% of all patients studied) were:

- Headache
- Increased amount of amylase (an enzyme used in digestion), in the blood without obvious signs of pancreatitis (inflammation of the pancreas)
- Tachycardia (fast heart beat)
- Decreased magnesium in the blood

It is possible for women of child bearing age to develop antibodies to BMP. In clinical experience, antibodies develop in approximately 1-5% of patients who receive the treatment. The effect of a mother's antibodies on an unborn baby is not known, both when the antibodies are detected and later. Women who are able to have children will need to take measures to prevent pregnancy for one year after treatment with BMP. Examples of birth control methods include, but are not limited to, birth control pills, intrauterine device (IUD), birth control implant, birth control patch and diaphragm. Your doctor can further discuss birth control options with you.

PREGNANCY: The following boxed warning is present on the current labeling for INFUSE® Bone Graft:

- In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Reduced ossification of the frontal and parietal bones of the skull was noted infrequently (<3%) in fetuses of rabbit dams immunized to rhBMP-2; however, there was no effect noted in limb bud development. There are no adequate and well-controlled studies in human pregnant women. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments.
- Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on human fetal development has not been assessed. In the clinical trial supporting the safety and effectiveness of the INFUSE Bone Graft in tibia fractures, 9/149 (6.0%) patients treated with INFUSE Bone Graft and 1/150 (0.7%) patients treated without exposure to rhBMP-2 developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive. Theoretically, re-exposure may elicit a more powerful immune response to BMP-2 with possible adverse consequences for the fetus. However, pregnancy did not lead to an increase in antibodies in the rabbit study. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that a lack of BMP-2 activity may cause neonatal death or birth defects. It is not known if anti-BMP-2 antibodies may affect fetal development or the extent to which these antibodies may reduce BMP-2 activity.
- INFUSE® Bone Graft should not be used immediately prior to or during pregnancy. Women of childbearing potential should be advised not to become pregnant for one year following treatment with the INFUSE® Bone Graft.
- The safety and effectiveness of the INFUSE® Bone Graft in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.

Safety data has not been established in females who are pregnant or nursing, and these patients will be excluded from this study. Females will undergo serum pregnancy testing in order to rule out pregnancy prior to implantation of INFUSE® Bone Graft. Informed Consent will inform subject's that INFUSE® Bone Graft has not been tested in pregnant or nursing women. Female

subjects with child-bearing potential will be advised to use oral contraceptives and/or refrain from becoming pregnant for 12 months following implantation. These precautions should minimize any potential risk to female patients and/or their fetus. If a subject becomes pregnant after implantation of INFUSE® Bone Graft the Investigator will document pregnancy as an AE, advise the subject to notify their obstetrical physician, monitor for occurrence of additional AEs, and report findings related to pregnant and/or nursing females in the annual and final report.

Risks Associated with Standard Treatment

The risk of standard treatment with iliac crest bone graft harvest includes infection, bleeding, donor site pain, and possible increased length of hospital stay.

Risks Associated with Both Treatments

With any surgical procedure, there is a small risk of having an infection in the bone, and small risk of having complications from anesthesia. This injury is severe and known to cause stiffness, pain, nerve paralysis, and physical limitations regardless of the treatment one receives. The following risks are related to the anesthesia/surgery used to place a bone graft and expected to be equal for both groups:

- Bowel, bladder or gastrointestinal problems
- Change in mental status
- Damage to blood vessels, bleeding (which may require a blood transfusion) or cardiovascular system compromise
- Damage to nearby tissues
- Development of respiratory problems
- Disassembly, bending, breakage, loosening and/or migration of IM nail components
- Incisional complications
- Neurological system compromise
- Pain or discomfort
- Side effects from anesthesia or the surgical approach
- Tissue or nerve damage

- *Sensitive Questions*. Some of the questions asked as part of this study may make participants feel uncomfortable. Participants may refuse to answer any of the questions, take a break or stop participation in this study at any time.
- *Loss of Confidentiality.* Any time information is collected; there is potential risk for loss of confidentiality.
- *Risks of Radiation from the Diagnostic Tests.* Radiation dose received from diagnostic tests is medically indicated for participant's condition and it is the same that they would get if they were not involved in this research study.
- *Risks of Blood Drawing* Risks associated with drawing blood from the arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting

also are possible, although unlikely. All patients will have about a tablespoon of blood drawn to rule out infection. Females of child bearing age will have an additional tablespoon of blood collected for a pregnancy test.

Steps to Minimize Risk

There may be unknown risks/discomforts involved. Study staff will update the participant's in a timely way on any new information that may affect the patient's health, welfare, or decision to stay in this study. The risks of participation in this study if one is randomized to the Rh-BMP 2 group are documented from previous studies. If there is an accelerated healing rate in those patients who receive rhBMP-2 versus the autograft, the patient benefits may include less pain, a decrease in the need for secondary interventions, and improved functional outcome. If there is no healing with the use of the Rh-BMP 2 group, the patient will still be able to receive autograft to promote healing.

The patient's physician and the study investigators will share responsibility for patient safety. They will ensure patient confidentiality throughout trial management. The investigator and designated study staff will be responsible for adhering to institutional standards for ensuring patient safety and confidentiality.

At each clinical visit, assessment will be made based on vital signs, physical evaluation of the limb including skin inspection, pain, swelling, infection, neurovascular status and radiographic evaluation of the involved tibia. There will be close monitoring of the occurrences of adverse events. In addition, certain vulnerable patient populations have been excluded from this study.

Every effort will be made to keep patient information confidential.
Retrieval Study
Should a patient fail to heal with the use of Bone Morphogenetic protein-2, salvage would be attempt of autogenous bone graft. As the sponge is dissolved within 14 days and the product thus would not be retrievable at salvage surgery.

Device Description

The INFUSE® Bone Graft component consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) soaked onto an absorbable collagen sponge (ACS) carrier. BMP-2 is a natural human protein that has been shown in animal studies to induce bone formation. The human BMP-2 protein sequence has been cloned and expressed in mammalian cells to yield large quantities of highly purified rhBMP-2.

INFUSE® Bone Graft is commercially available for use with the LT-CAGE® Lumbar Tapered Fusion Device in anterior lumbar spine interbody fusion procedures (P000058), for use in acute open tibial shaft fractures (P000054), and for use in sinus augmentations and localized alveolar ridge augmentations for defects associated with extraction sockets in oral maxillofacial procedures (P050053).

The carrier component, the absorbable collagen sponge (ACS), provides the matrix for the delivery of rhBMP-2. The ACS is commercially available and is marketed by Integra Life Sciences Corporation under the trade name HELISTAT® Absorbable Collagen Hemostatic Agent. That product is covered by a U.S. Food and Drug Administration Premarket Approval Application and is "approved for use in surgical procedures (other than neurological, ophthalmological, and urological surgery) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical" (Colla-Tec, Inc. – an Integra Life Sciences Company).

For the purposes of this study, a commercially-available INFUSE® Bone Graft (rhBMP-2/ACS) Large II kit (Ref. #7510800) will be used for the investigational group. The rhBMP-2 is provided as a lyophilized powder in vials delivering 12 mg of protein. After appropriate reconstitution, the concentration of rhBMP-2 is 1.50 mg/mL. The solution is then applied to the provided absorbable collagen sponge. INFUSE Bone Graft is prepared at the time of surgery and allowed a prescribed amount of time (no less than 15 minutes) before placement at the fracture site. Investigational patients will receive freeze-dried allograft chips (15 cc) wrapped in the rhBMP-2 soaked collagen sponge. Freeze-dried allograft chips will be obtained from the local/regional tissue bank at each site.

The INFUSE® Bone Graft kit contains the following components:

- One (1) vial of sterile rhBMP-2 (12mg);
- One (1) package of one (1) sterile ACS 3" x 4" (7.5 cm x 10 cm);
- One (1) vial of sterile water for injection (10 mL);
- Two (2) sterile 10 mL syringes with 20G 1 ½" needles;

Monitoring Procedures

This study is being conducted under the umbrella of the Major Extremity Trauma Research Consortium (METRC). The Consortium has developed an independent Data Safety Monitoring Board (DSMB) charged with the task of safety monitoring of all Consortium studies.

At its first meeting the DSMB will review definition of all outcomes, adverse events and serious adverse events and revisions to the protocol will be made as appropriate. Summary data on adverse events (together with study outcomes) will be monitored by the DSMB at its semiannual meetings or more frequently, as needed. These summaries will include analyses comparing rates of adverse events by blinded treatment group, by clinic, or in other subgroups requested by the DSMB.

After each meeting, the DSMB will issue a written summary of its review of the study data, including adverse events, for transmission to the IRBs at Johns Hopkins Bloomberg School of Public Health and each of the study centers.

The MM is responsible for providing medical guidance and overseeing patient safety for the pTOG clinical research study. The MM participates in determining the course of action necessary to meet the goals and objectives of the DSMB. This is achieved through the review of safety reports; resolving safety issues; interacting with Principal Investigators, and reporting to the DSMB.

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Plan for reporting unanticipated problems/adverse events:

Adverse Event ("AE"), Serious Adverse Event ("SAE") and Unanticipated Adverse Event ("UAE") monitoring will be conducted at all intervals (including those additional intervals not mandated by the protocol).

AE will be defined as any adverse event, whether or not that event is felt to be implant related, occurring at the time of or following time of implant through the remainder of study. AE's will be treated in accordance with accepted medical standards and documented in the subject's study binder and monitored by the Investigator and research team. AE's will be reported to the FDA and the site IRB in the annual report and the final report.

SAE will be defined as any significant adverse experience, including death or those events which may be either life-threatening or involve permanent or long term injuries, but excluding injuries that are non life-threatening and that are temporary and reasonably reversible. SAE's will be treated in accordance with accepted medical standards and documented in the subject's study binder and reported to the site IRB, the sponsor and Medtronic Customer Service Division (1-800-933-2635) within 1 business day of known occurrence. SAE's will be included in the annual and final report.

UAE will be defined as any event that could not be reasonably foreseen or had not been previously reported by MSD in the product package insert as a potential adverse event related to use of implant. UAE's will be treated in accordance with accepted medical standards and reported to the site IRB, the sponsor and Medtronic Customer Service Division (1-800-933-2635) within 5 business days after the Principal becomes aware of the event. UAE's will also be included in the annual and final report.

Unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study and all volunteer deaths related to participation in the study will be promptly reported by phone (301-619-2165), by e-mail (hsrrb@amedd.army.mil), or by facsimile

(301-619-7803) to the U.S. Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RPH, 504 Scott Street, Fort Detrick, Maryland 21702-5012

Department of Defense Reporting Requirements

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

(1) The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

(2) Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

(3) All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

(4) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

(5) Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

(6) Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

(7) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

(8) The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

Payment:

Participants will receive $10 for the first four follow up visit, and $25 for completing the final two visits at -6 and 12 months after surgery in appreciation for their time and effort.
There are no additional costs for participating in this research study outside of standard of care. The patient and their insurance company will be billed for standard of care costs for treating an open tibia fracture with bone loss (i.e. rehospitalization and surgical procedure to address the bone loss). The Rh-BMP 2 will be provided should the patient randomize to this study arm and neither the patient, nor their insurance company will be billed for the device.

The Rh-BMP2 is being provided at no cost to the patients randomized to that group. INFUSE® Bone Graft is a currently approved medical device marketed by Medtronic Sofamor Danek USA, Inc. INFUSE® Bone Graft (rhBMP-2/ACS) will be provided by Medtronic free of charge for all investigational participants, this therefore does not constitute commercialization of the device.