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Supplement 1

A Prospective Randomized Trial to Assess Fixation Strategies for Severe Open Tibia Fractures: Modern Ring External Fixators vs. Internal Fixation (FIXIT Study)

Protocol

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FIXIT Design Synopsis

Title: A Prospective Randomized Trial to Assess Fixation Strategies for Severe Open Tibia Fractures: Modern Ring External Fixators vs. Internal Fixation (**FIXIT** Study)

Sponsor: DOD OETRP

Type of study: Phase III randomized clinical trial

Objectives: Our goal is to perform a multi-center randomized controlled trial of the use of modern ring external fixation versus internal fixation for fracture stabilization of severe open tibia fractures.

Primary Aim: To compare the outcomes associated with modern ring external fixators versus standard internal fixation techniques in treating "severe" open tibia shaft or metaphyseal fractures with or without a bone defect of any size.

Primary Hypothesis: Among patients with open tibia shaft or metaphyseal fractures (with or without a bone defect of any size), the rate of re-hospitalization for major limb complications will be lower for patients treated with ring fixators than those treated with standard internal fixation.

Secondary Hypotheses*:* Among patients with open tibia shaft or metaphyseal fractures (with or without a bone defect of any size), the overall rate of infections will be lower for patients treated with ring fixators than those treated with standard internal fixation. Measures of fracture healing, limb function, and patient reported outcomes (including pain) will be as good or better among patients treated with ring fixators than those treated with standard internal fixation.

Secondary Aim #1: To determine the percentage of Gustilo IIIB open tibia shaft fractures that can be treated successfully (i.e. without amputation) without a soft tissue flap secondary to the use of ring external fixators.

Secondary Aim #2: To determine the two-year treatment costs associated with fixation of "severe" open tibia shaft or metaphyseal fractures (with or without a bone defect of any size) using modern ring external fixators versus standard internal fixation techniques.

Secondary Aim #3: To determine patient reported levels of satisfaction with the fixation method and overall treatment and to compare satisfaction between the two treatment groups.

Study design: Multicenter, prospective randomized controlled trial. Patients who refuse randomization will be eligible for a prospective cohort study.

Treatment groups:
Group 1: Definitive fixation with a modern ring fixator.
Group 2: Definitive fixation with a locked intramedullary nail or plate.

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Study duration: 6 years (6 month planning, 36 month accrual, 24 month final follow-up, 6 month analysis and writing). Participants will be followed for two years from the time of injury.

Sample size: 312 in randomized study and 312 in observational study.

Number of study sites: Between 20 and 25 sites

Inclusion criteria

1. All open tibia fractures meeting at least one of 1 the following criteria:
    a. Diaphyseal or metaphyseal Type IIIB (Gustilo IIIB Fractures are open fractures that require either a rotational or free flap for coverage of a soft tissue defect).
    b. Diaphyseal or metaphyseal Type IIIA where extensive contamination or muscle damage (e.g. all military injuries from IED) precludes nail/plate placement at first debridement.
    c. Diaphyseal or metaphyseal Type IIIA, where injury would have been classified as a IIIB, but because enough muscle was removed, the skin could be closed.
    d. Diaphyseal or metaphyseal Type IIIA, where after debridement, bone gap is greater than 1cm.
    e. Diaphyseal or metaphyseal Type IIIA, where fasciotomies were performed for impending or diagnosed compartment syndrome, and wounds could not be closed primarily (i.e. needs skin grafting).
2. Ages 18 – 64 years inclusive
3. Study fracture is suitable for limb salvage using either a modern ring external fixator or internal fixation (internal fixation =locked intramedullary nail or plate).
4. Patients *may* have co-existing non-tibial infection, with or without antibiotic treatment.
5. Patients *may* have risk factors for infection including diabetes, immunosuppression from steroids or other medications, HIV, or other infections.
6. Patients *may* have a traumatic brain injury.
7. Patients *may* have other fractures including spine, upper extremity fractures, contralateral lower extremity injuries, ipsilateral pelvis, hip, femur or foot injuries.
8. Patients *may* be treated initially with a temporary external fixator prior to randomization.
9. Patients *may* be treated initially at an outside institution prior to transfer to the study institution, as long as the definitive fixation was not performed prior to entrance into the study.
10. Patients with bilateral injuries that meet inclusion criteria *may* be included, but only the limb rated as "more severe" by the treating surgeon will be enrolled in the study.
11. Fractures *may* have a gap after debridement of any size, including no gap.

Exclusion criteria

1. Patients presenting with a traumatic amputation of the tibia
2. Patients already received definitive fixation with an IM nail, plate or ring fixator prior to study enrollment
3. Tibia already infected as diagnosed by a surgeon and currently receiving treatment for it
4. Patient speaks neither English nor Spanish

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5. Patient is a prisoner
6. Patient has been diagnosed with a severe psychiatric condition
7. Patient is intellectually challenged without adequate family support
8. Patient lives outside the catchment area
9. Non-ambulatory patient due to an associated complete spinal cord injury
10. Non-ambulatory before the injury due to a pre-existing condition.
11. Complex pilon and plateau fractures. The study tibiafracture may have extension into the joint surface, but should primarily be a metaphyseal or diaphyseal fracture and not have an ipsilateral tibial plateau or pilon fracture. Contralateral tibial plateau and pilon fractures are allowed

NOTE: Patients must meet all inclusion/exclusion criteria to be eligible for enrollment in the prospective cohort study if the patient refuses enrollment in the randomized controlled trial.

Outcome measures

Primary: Hospital re-admission for complication is defined as any re-admission to the hospital secondary to the treatment of the open tibia fracture for a defined set of complications. The list of complications includes: amputation, infection, flap failure, non-union, mal-union, loss of reduction, or hardware failure.

Secondary: Infection (superficial or deep), fracture healing; limb function, pain intensity and interference, and patient reported functional outcome and quality of life. Cost of treatment (for the initial hospitalization and total one-year treatment costs) will also be ascertained as will patient reported satisfaction with fixation method and overall treatment.

Randomization: Randomization in variable permuted blocks, stratified by clinical center Randomization will be administered centrally by the Data Coordinating Center through the REDCap electronic database.

Statistical analysis: All analyses will be both on an "intention-to-treat" and "as treated" basis.

Safety monitoring: An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety, review efficacy, evaluate recruitment, and assess overall data quality

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1. Primary Hypothesis and Principal Objective

Severe open fractures of the tibia (shin) bone are difficult to treat and are associated with high rates of infection and other complications. There is controversy regarding the best treatment, particularly in fractures with large wounds from trauma. The two current standard treatment options are to place an internal fixation device (a nail or plates with screws) or to use a device with pins that stick out of the skin and attach to rings outside the body (modern ring external fixator). It is unknown which of these standard of care treatment options will result in lower complication rates and better function of the leg.

The principal objective of this randomized controlled trial is to compare these two treatments in fractures with both large and small bone defects to determine which treatment will provide the best outcomes for patients. We hypothesize that among patients with severe open tibia shaft fractures (with or without a bone defect of any size), the rate of re-hospitalization for complication will be lower for patients treated with modern ring fixators than those treated with internal fixation.

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2. Background and Significance

2.1. Definition of the Problem. High energy open tibia fractures are common military injuries [11,12,13 ,14] that present a significant clinical challenge [1,2,3,4,5,6,4,7,8,9,10]. As with high-energy civilian open tibia fractures, a high rate of hospital re-admission for complication has been observed, and these complications have been linked to poor longer term outcomes [1,15]. Traditional treatment protocols for high energy tibia fractures have demonstrated rates of surgical site infection and osteomyelitis ranging from 14.3%% - 60.0% [1, 6,4,5,7, 16, 8] in both military and high energy civilian settings. The Lower Extremity Assessment Project (LEAP) study reported that the re-hospitalization rate for complications after severe open tibia fractures is as high as 57% [1]. Traditional treatment protocols typically utilize intramedullary nails or plates for fracture fixation, which have the disadvantage of placing metal (the nail or plate) within the fracture site. Multiple studies demonstrate that infection rates tend to increase whenever hardware is placed within a wound [17,18], likely due to the difficulty the immune system has in clearing bacteria from the biofilm that develops on metallic surfaces [17,19]. High energy military injuries have a particularly high risk of infection, further increasing the relative theoretical risk of traditional IM nails or plates, and are complicated by large bone defects in approximately 20% of the cases [1].

2.2 Modern Ring External Fixators. New technologies and fixation strategies are emerging that have the potential to reduce hospital re-admissions and infections as well as to improve functional outcomes. One of the most promising new technologies is the use of modern ring external fixation that allow sequential adjustments to re-align the limb during recovery [20]. This technique is currently FDA-approved, but as of yet have not been rigorously studied in this high-energy patient population or in comparison to traditional internal fixation methods.

The use of modern ring external fixation may be appealing in patients with high energy open tibia fractures. Unlike tibial nails or plates, ring external fixation does not place any hardware at the fracture site. Instead, percutaneous pins placed away from the open wounds and attached to carbon fiber rings provide fracture stability [20]. New ring fixators also offer improved stability over older traditional external fixators that were plagued with malunions, non-unions, and limitations in patient mobility [21].

Recently, two small retrospective series conducted at U.S. military centers have provided provocative evidence that ring external fixators may lower infection rates with high energy open tibia fractures sustained in combat. Lacap *et. al*. [7] demonstrated an infection rate of 14.3% using tibial nails as stabilization, whereas Keeling *et. al*. [4] demonstrated an infection rate of only 3% (roughly a five fold decrease) using the same soft tissue management protocol but ring external fixators as the method of fixation. These findings are similar to Lerner et al.'s report of a 1.6% deep infection rate treating a variety of military open fractures using ring fixators [16]. These studies were limited by retrospective design, small sample size and lack of control groups. One small prospective trial comparing ring fixation to IM nails for open tibia fractures has been performed, but the study was underpowered (only 32 patients per arm) and did not include "severe" open fractures (tibias that need a flap for limb salvage (Gustilo IIIB [22,23])) so its application to the military population is limited [6]. However in another small prospective study of patients with grade IIIB and IIIC fractures (n=69), ring fixation resulted in a 100% union rate with no deep infection or osteomyelitis (Hutson, abstract presented at the Orthopaedic Trauma Association annual meeting, 2009).

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Modern ring fixators may have an additional advantage over intramedullary nails in that they offer controlled adjustment of the alignment of the limb. The continuous adjustment of fracture alignment during healing has been previously utilized for limb lengthening and treatment of large bone defects using a process known as "distraction osteogenesis" [24,25,26,27,28,29,30,31,32,33,34,20,35]. Advocates of this technique use it to treat large bone defects by creating an osteotomy (breaking the bone) at a site away from the fracture and transporting the existing bone into the defect. New bone forms at the osteotomy site, thus maintaining the length of the limb and avoiding bone grafting procedures.

The ability to perform continuous deformity correction also has potential to reduce the need for flap coverage in severe fractures that normally would require a flap. Plastic surgeons are typically needed to transfer muscles from the leg, thigh or abdomen into soft tissue defects in order to cover the bone and promote vascularity. This additional surgery is associated with morbidity at the donor site, increased surgical costs, poor surgical site cosmesis, and a need for timely reconstructive plastic surgery intervention. Using modern external fixation, leaders in this field are shortening limbs and performing "soft tissue reductions" resulting in closure of wounds that otherwise would need a flap. Once the wounds are healed, the soft tissues are stabilized, and the traumatic inflammatory response is diminished, the osseous anatomy can be restored by lengthening and properly aligning the limb, thus converting Gustilo IIIB fractures into Gustilo IIIA fractures. Although this technique is being used in some military centers [26,34], it has yet to be rigorously studied.

2.3 Study Rationale. Although there is strong theoretical data and some promising clinical data, it is not yet clear that modern ring fixators will perform better than the current standard nails in a rigorous head to head trial. The use of older external fixators for high energy trauma has historically been associated with poor outcomes such as mal-union [36], so it remains to be proven that newer ring fixators can overcome these problems. It is possible that although modern ring external fixators will likely reduce the deep infection rate, perhaps it will negatively impact functional outcomes secondary to the long duration of time required for fracture defect healing with the frame in place. The literature provides no data to guide clinicians in this regard.

Ring fixators offer a technology and treatment pathway that is very different from either intramedullary nails or plate fixation after high energy tibial factures. As such, it will be particularly important to not only study re-admission and infection rates, but also functional outcomes. As with previous studies of high energy lower extremity trauma [1], validated outcome measures will be needed to fully evaluate how the use of these technologies impacts patients' lives.

High energy, military type injuries are relatively rare. In order to perform the study with adequate power, multiple centers treating many high-energy tibial fractures and experienced with all treatment modalities are required for the study. As such, the proposed study will be performed using the member centers of the METRC Consortium. The study design of prospective randomized trial should provide the highest quality data to attain the specific study aims. Patients who decline randomization will be asked to enter into a prospective arm and followed as described in other randomized surgical trials, such as the SPORT trial [37,38, 39].

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The study is designed to evaluate 1 year treatment outcomes, however, patients will be followed for 2 years after injury. Data collected during the second year of follow-up will allow us to examine the longer term outcomes of treatment for these injuries.

2.4 Study Significance. The results of this study will be of significant importance to the military, since high energy open tibia fractures are common in current conflicts and are associated with high complications and poor outcomes [11,12,13,14]. Similarly, the results will be of great utility to surgeons treating high-energy civilian patients. If the study hypotheses are supported, this well-powered multicenter study will likely influence clinical practice by shifting treatment from the most common current treatment (internal fixation) towards modern ring external fixation for severe open tibia fractures. This major change in philosophy in the orthopaedic trauma community would be revolutionary and ground breaking. This multicenter study offers great potential to make significant improvements to the care of military battlefield injuries [11,12,13,14].

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3. Study Design

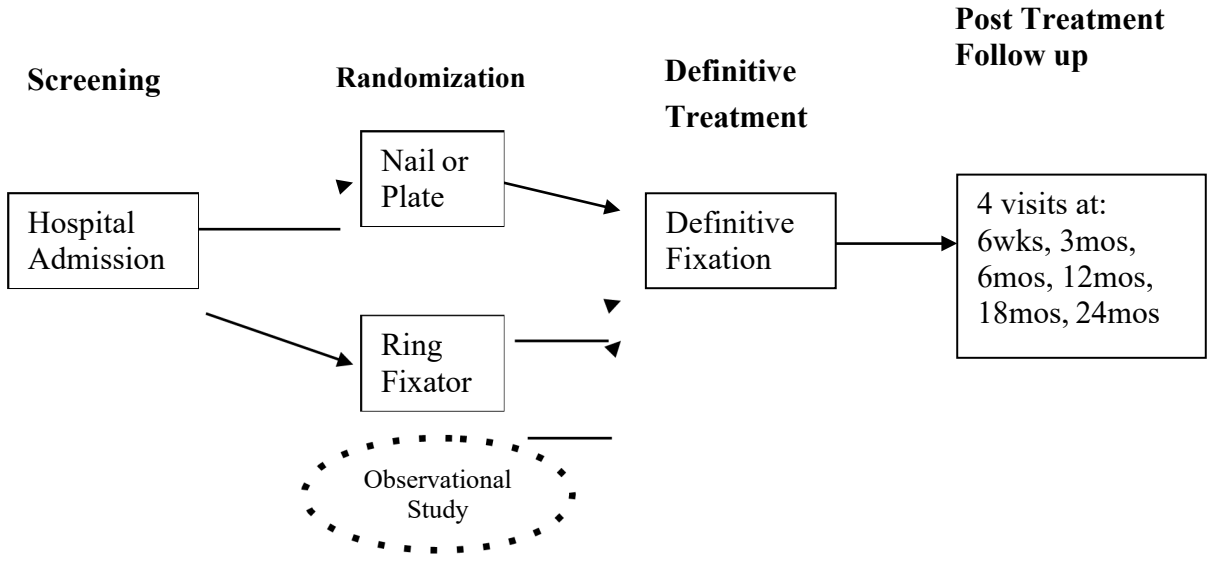
3.1. Design overview

The FIXIT study is a multi-center, prospective randomized controlled trial of modern ring external fixation techniques versus internal fixation in "severe" open tibia fractures that are most similar to war injuries. The primary hypotheses for the study will be tested in all "severe" open tibial shaft fractures (regardless of presence or size of bone defect) and will compare modern ring fixators to locked intramedullary nails (IM nails) or plates.

Patients will be randomized to one of the 2 treatment groups prior to the time of definitive fixation. The success of the study hinges on an ability to successfully enroll and randomize patients. This study is more challenging than most as the two treatment arms will likely be perceived as different to the patients, potentially lowering patient willingness to be randomized. To promote a higher enrollment rate, the consent protocol will directly involve the patient's treating surgeon (discussed below). Even with these efforts, there will likely be a significant number of patients who refuse randomization but are willing to participate in the study. These patients will be enrolled in a prospective cohort study as has been done in other large surgical randomized studies.

Patients will be followed 6 weeks, 3, 6, 12, 18 and 24 months after injury. The primary outcome is hospital readmissions for complications. Secondary outcomes include infection, functional outcome, and patient reported outcomes. Acute hospitalization as well as one-year treatment costs will also be ascertained and compared between the two treatment groups. A schematic of the trial design is presented below.

Figure 1: Trial Design



3.2. Treatment groups

Patients who meet the eligibility criteria and have signed an informed consent statement will be

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randomly assigned to one of two groups:

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Group 1: Definitive fixation with a ring fixator.
Group 2: Definitive fixation with a locked IM nail or plate.

Randomization will provide patients a 50/50 opportunity to be in either group. The randomization scheme will assign patients in randomly permuted blocks of assignments stratified by clinical center. Investigators will be blinded to block size. This scheme will ensure that the two groups will be balanced by calendar time of enrollment (to minimize secular effects) and by clinic (to minimize clinic-specific effects of differences in patient populations and management).

The randomization plan will be prepared and administered centrally by the Coordinating Center (CC) but will not require real time interaction with a CC staff member. Requests for randomizations will be made by the centers using a secure web-based application. An assignment will be issued only if the database shows that the patient is eligible and the consent statement has been signed.

3.2.1 Treatment Group 1: Fixation with Ring Fixator.

Description: Several modern ring fixators are currently FDA-approved but have not been rigorously studied in this high-energy patient population or in comparison to traditional internal fixation methods. Unlike tibial nails or plates, ring external fixation does not place any hardware at the fracture site. Instead, percutaneous pins placed away from the open wounds and attached to rigid rings provide fracture stability.

For this study we define “modern ring external fixator” as any fixator that has at least 1 ring proximal and 1 ring distal to the fracture site. The rings may be connected to the tibia using any combination of external fixation pins or wires at the surgeon’s discretion. There must be at least two pins or wires connected to each ring, and typically there will be at least three pins or wires. Any FDA approved ring fixator meeting this definition from any manufacturer is allowed.

Some modern ring fixators also allow sequential adjustments to re-align the limb during recovery. The continuous adjustment of fracture alignment during healing has been previously utilized for limb lengthening and treatment of large bone defects using distraction osteogenesis. The ring fixator may or may not have the capacity for distraction osteogenesis, depending on surgeon preference and the specifics of the treatment plan. Fractures with bone defects may be treated with either distraction osteogenesis or delayed bone grafting at the preference of the treating surgeon.

Patients with bone defects that are treated using distraction osteogenesis will use standard techniques, with minor details of the process left to the discretion of the treating surgeon. Typically, once soft tissue coverage has been completed, a corticotomy (surgical breaking of the bone) is performed at a distance from the fracture site. Lengthening (“distraction”) occurs at a rate of 1mm/day and moves the intact bone to fill the defect, while creating new bone at the corticotomy site (“osteogenesis”). Once the bone has filled the defect site, the newly formed bone (“regenerate”) consolidates. Frames are removed once the regenerate has consolidated adequately, either in the office or in the operative suite. Unrestricted weight bearing without support is usually allowed early on in the course of treatment.

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Patients with bone defects that are treated with delayed bone grafting will use standard protocols, with details left to the discretion of the treating surgeon. Defects will typically be treated with antibiotic impregnated polymehthyl methatcralate spacer to induce a vascularized "biomembrane" around the bone defect. Four to six weeks later the biomembrane is opened, the spacer removed, and the void is filled with bone graft. The type of graft, how it is harvested, and the use of bone morphogenic proteins to augment the healing will be at the discretion of the treating surgeon, consistent with current clinical practice.

Some patients who randomize to the ring external fixator may be judged by the treating surgeon to potentially not require a flap if the limb were shortened acutely and then lengthened again once the soft tissue has stabilized. The decision to attempt this technique will be left to the treating surgeon, as will all other technical details of the two treatment arms.

Rationale: Points establishing a rationale for the use of ring fixators in the treatment of severe open tibia fractures are:

- Ring external fixation does not place any hardware at the fracture site, with the potential for reducing infections.
    - Two small retrospective series conducted at U.S. military centers have provided provocative evidence that ring external fixators may lower infection rates with high energy open tibia fractures sustained in combat.
- Modern ring fixators offer improved stability over older traditional external fixators that were plagued with malunions, non-unions, and limitations in patient mobility.
- Some modern ring fixators, have an additional advantage over internal fixation in that they offer sequential adjustment of the alignment of the limb. The continuous adjustment of fracture alignment during healing has been previously utilized for limb lengthening and treatment of large bone defects using a process known as "distraction osteogenesis"
- The ability to perform continuous deformity correction also has potential to reduce the need for flap coverage in severe fractures that normally would require a flap.

Potential Adverse Effects. There are no potential adverse effects specific to the use of a modern ring fixator compared to the use of a nail or plate. There are, however, several potential adverse effects common to all known treatments of severe open tibia shaft fractures. Most of these adverse effects are being examined as specific outcomes in the proposed study (i.e. infection, flap failure, amputation, non-union, malunion, loss of reduction, or hardware failure). Other potential adverse effects include:

- An adverse reaction, side effect, occurrence of toxicity, or sensitive reaction in excess of expectations;
- Pulmonary embolism;
- Death

3.2.2. Treatment Group 2: Internal Fixation with Nail or Plate

Description: Patients who are randomized to internal fixation will receive either a locked IM nail or plate at the discretion of the operating surgeon. Although this introduces some heterogeneity into the internal fixation group for this treatment arm, we believe it is a necessary compromise given the rarity of

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these injuries in the civilian setting coupled with the technical challenge these injuries present in war injuries.

Eligible patients with tibial diaphyseal fractures will typically receive a standard locked IM Nail with minor details of the treatment determined by the treating surgeon. The nail must use at least one static interlock proximal to and one static interlock distal to the fracture site. The nail may be placed with either a reamed or unreamed technique. The FDA-approved nail may be from any manufacturer.

Methaphyseal fratures, especially those with fracture lines extending into the joint may be more commonly treated with plate fixation. The details of the plate application will be determined by the treating surgeon. The plate system must be FDA-approved, but can be from any manufacturer. The plate may be applied in an open or percutaneous fashion. Any combination of locked and/or non-locked screws may be used.

For those patients who receive internal fixation, massive bone defects will be treated with delayed bone grafting using standard protocols. Defects will typically be treated with antibiotic impregnated polymehthyl methatcralate spacer to induce a vascularized “biomembrane” around the bone defect. Four to six weeks later the biomembrane is opened, the spacer removed, and the void is filled with bone graft. The type of graft, how it is harvested, and the use of bone morphogenic proteins to augment the healing will be at the discretion of the treating surgeon, consistent with current clinical practice. Weight bearing and minor details of the procedures will be at the discretion of the treating surgeon.

Rationale: Points establishing a rationale for the use of internal fixation in the treatment of severe open tibia fractures are:

- All orthpaedic trauma surgeons are familiar with the use of internal fixation in the treatment of severe tibia fractures and it is the most commonly performed treatment for these injuries.
- If deep infection does not occur, then the likelihood of minor infection (which is common with ring fixator pin tract infections) is much lower.
- Since all of the hardware is contained within the skin the patient does not have the challenge of ambulating with a bulky, heavy ring external fixator on the limb.
- Internal fixation does not use external fixation pins which may limit muscle motion and promote stiffness.

Potential Adverse Effects. There are no potential adverse effects specific to the use of a modern ring fixator compared to the use of a nail or plate. There are, however, several potential adverse effects common to all known treatments of severe open tibia shaft fractures. Most of these adverse effects are being examined as specific outcomes in the proposed study (i.e. infection, flap failure, amputation, non-union, malunion, loss of reduction or hardware failure). Other potential adverse effects include:

- An adverse reaction, side effect, occurrence of toxicity, or sensitive reaction in excess of expectations;
- Pulmonary embolism;
- Death

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The devices used are in common clinical use so adverse reactions, side effects, toxicity, and sensitivity reactions are anticipated to be a very rare event. Death is anticipated to be a relatively rare adverse event as survival rates at major civilian trauma centers are typically above 95%. Pulmonary complications will also likely be relatively uncommon as patients who sustain major trauma develop pulmonary embolism in <10% of cases. Neither of these events is suspected to be related to treatment of the tibia fracture.

3.3 Standardization of Perioperative Treatments across Centers

The clinical course of the patients in both arms of the study will follow the universal protocols for treating skeletal injuries as is already standard practice at all trauma centers. [40] All patients will receive antibiotics upon presentation as is standard in the treatment of open fractures. Prophylaxis against thrombo-embolic disease will be used using each institution's protocol. Minor variability in practices, such as duration of postoperative antibiotics, type of antibiotics, immobilization, duration until weight bearing is allowed, will all be at the discretion of the operating surgeon. This may impart some variation in care across the centers, but will realistically mimic the current state of the art for the best care possible in each of the treatment arms. Randomization within centers will also help to minimize the potential bias introduced by differences in practice. Further, relevant details regarding treatment of both the study injury and associated injuries will be recorded and used in the analysis as necessary to balance comparisons between groups.

3.4. Training and Certification of Centers

Centers vary in their experience with the use of ring external fixation for severe tibia shaft fractures, although almost all centers have at least one surgeon who has some experience with the technique. All surgeons who will be applying ring fixators at participating sites must have either:

- Completed a formal training course in ring fixation;
- Have significant previous experience in applying fixators (defined as having completed more than 5 cases); or
- Operate at a center that has a surgeon with significant previous experience (> 5 cases) who has indicated a willingness to serve as a mentor for other surgeons who have not completed the formal training.

Prior to initiation of the study (and as part of the center certification process), prior experience in using ring fixators of all participating surgeons will be documented. A training course will be sponsored by the METRC Steering Committee prior to initiation of the study. This training will be open to all surgeons at participating FIXIT sites. At least one surgeon from each participating site must attend a training session regardless of experience. Exceptions will be made for centers who have extensive experience on a case by case basis.

All centers participating in FIXIT together with their respective study personnel will undergo certification per policies and procedures of METRC.

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4. Patient Selection

4.1. Overview and Clinical Centers

Approximately 624 patients will be recruited from the METRC core clinical centers, military treatment facilities and satellite centers over a 2.5-year period. We anticipate that 312 will be randomized to one of the two treatment arms. The other 312 will participate in the observational study. The core centers are level I trauma centers with large numbers of severe open tibial fractures and include sites with a proven track record for prospective study of high energy tibial shaft fractures. Satellite centers are trauma centers with smaller patient volumes and have varying amounts of experience in prospective studies of orthopedic trauma (although all have some experience). All participating centers have expertise in use of IM nails, complex limb salvage including large bone defects, as well as plastic surgery support needed for difficult limb salvage. Almost all centers have at least one surgeon with experience using ring fixators (see Section 3.4 above).

Eligible patients will be identified and recruited at the participating clinical centers subject to the inclusion and exclusion criteria listed below.

The Coordinating Center will develop a master recruitment plan and work with individual centers to customize this master plan to meet the needs of individual centers (see Section 5.2). Recruitment goals will be set for each individual center and monitored on an ongoing basis.

4.2. Inclusion criteria

In order to qualify for inclusion in the trial, patients must satisfy the following inclusion criteria:

1. All open tibia fractures meeting at least one of 1 the following criteria:
    a. Diaphyseal or metaphyseal Type IIIB (Gustilo IIIB Fractures are open fractures that require either a rotational or free flap for coverage of a soft tissue defect).
    b. Diaphyseal or metaphyseal Type IIIA where extensive contamination or muscle damage (e.g. all military injuries from IED) precludes nail/plate placement at first debridement.
    c. Diaphyseal or metaphyseal Type IIIA, where injury would have been classified as a IIIB, but because enough muscle was removed, the skin could be closed.
    d. Diaphyseal or metaphyseal Type IIIA, where after debridement, bone gap is greater than 1cm.
    e. Diaphyseal or metaphyseal Type IIIA, where fasciotomies were performed for impending or diagnosed compartment syndrome, and wounds could not be closed primarily (i.e. needs skin grafting).
2. Ages 18 – 64 years inclusive
3. Study fracture is suitable for limb salvage using either a modern ring external fixator or internal fixation (internal fixation =locked intramedullary nail or plate).
4. Patients *may* have co-existing non-tibial infection, with or without antibiotic treatment.
5. Patients *may* have risk factors for infection including diabetes, immunosuppression from steroids or other medications, HIV, or other infections.
6. Patients *may* have a traumatic brain injury.

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7. Patients *may* have other fractures including spine, upper extremity fractures, contralateral lower extremity injuries, ipsilateral pelvis, hip, femur or foot injuries.
8. Patients *may* be treated initially with a temporary external fixator prior to randomization.
9. Patients *may* be treated initially at an outside institution prior to transfer to the study institution, as long as the definitive fixation was not performed prior to entrance into the study.
10. Patients with bilateral injuries that meet inclusion criteria *may* be included, but only the limb rated as "more severe" by the treating surgeon will be enrolled in the study.
11. Fractures *may* have a gap after debridement of any size, including no gap.

4.3. Exclusion criteria

Patients who satisfy any of the following exclusion criteria will be ineligible for enrollment in the trial:

1. Patients presenting with a traumatic amputation of the tibia
2. Patients already received definitive fixation with an IM nail, plate or ring fixator prior to study enrollment
3. Tibia already infected as diagnosed by a surgeon and currently receiving treatment for it
4. Patient speaks neither English nor Spanish
5. Patient is a prisoner
6. Patient has been diagnosed with a severe psychiatric condition
7. Patient is intellectually challenged without adequate family support
8. Patient lives outside the catchment area
9. Non-ambulatory patient due to an associated complete spinal cord injury
10. Non-ambulatory before the injury due to a pre-existing condition.
11. Complex pilon and plateau fractures. The study tibiafracture may have extension into the joint surface, but should primarily be a metaphyseal or diaphyseal fracture and not have an ipsilateral tibial plateau or pilon fracture. Contralateral tibial plateau and pilon fractures are allowed

NOTE: Patients must meet all inclusion/exclusion criteria to be eligible for enrollment in the prospective cohort study if the patient refuses enrollment in the randomized controlled trial.

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5. Trial protocol

5.1. Overview

The patient-related activities of the FIXIT trial can be divided into the following phases:

- Phase 1: Screening for eligibility (as early as possible during initial hospitalization and before definitive surgery);
- Phase 2: Consent of patient to be randomized into one of the two treatments (before definitive surgery); for those not randomized, consent into the observational study;
- Phase 3: Randomization to treatment (prior to the time of definitive surgery);
- Phase 4: Treatment and baseline data collection phase (application of external fixation or internal fixation device and perioperative treatment);
- Phase 5: Post-treatment follow-up phase (6 weeks, 3, 6, 12, and 18 months following injury).

The visit and data collection schedule described below in detail is summarized in Appendix 9.2

5.2. Phase 1: Screening for eligibility

Patients will be screened for eligibility in each center by the local research coordinator in close coordination with the surgeon co-investigators. Screening will typically occur within the first day or two after the initial debridement and placement of a temporary external fixation and prior to definitive fixation. All potentially eligible patients will be entered into REDCap, a study number assigned, and eligibility criteria confirmed. The coordinating center together with the Adjudication Committee will be available to adjudicate eligibility.

5.3 Phase 2: Consent and Enrollment

After eligibility is confirmed by the Site Investigator, patients will be approached for their consent to participate in the randomized controlled trial. Informed consent will be obtained prior to definitive fixation. Typically, patients are initially placed into an external fixator to facilitate serial washouts, and not converted to internal fixation until the wound bed is judged to be adequately debrided (typically 2-7 days after placement of the external fixator). As such, the vast majority of patients will be enrolled after the initial surgery, thus facilitating participation in the randomized portion of the study. For the rare case where the surgeon deems the wound is clean enough to be treated at the initial surgery with a nail or ring fixator, consent must be obtained prior to the first surgery to include the patient in the randomized arm of the study. If consent is not obtained prior to the initial surgery, the patient will not be eligible to participate in either the randomized controlled trial or the observational study.

To encourage a high level of participation from eligible patients, the attending surgeon will be involved in the consent conversation. The conversation will be initiated by the research coordinator and surgeon together. The consent process will involve a scripted dialogue and make use of several materials to be developed for the FIXIT study. Specifically, patients and their families will be provided with a pamphlet describing the study, the risks and benefits of participation and what will be expected of them if they

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choose to participate. A mini-flip chart will also be made available for use by the research team to describe the study and what it means to participate in the study.

A brief video will be used to standardize a description of the two techniques under study. This video will be played with the patients /family and provided as a DVD for the patients to take away with them. Saw bones will also be provided to all centers for the surgeon to use in explaining the procedures.

All recruitment materials will be provided in both English and Spanish.

If the patient refuses to be randomized, then (and only then) will he or she be asked for consent to participate in the observational arm of the study. If the patient refuses to be randomized but agrees to participate in the observational study, the treatment choice will be left to the patient and his or her surgeon

Once consented into the RCT or observational study, baseline data regarding patient characteristics, injury characteristics, fracture classification and medical history/ co-morbidities will be collected and entered in to the REDCap data collection system. Some of this information will be obtained via a brief interview with the patient or his/her surrogate.

5.4. Phase 3: Randomization

Once the eligibility of the patient for study inclusion has been determined and the patient has been consented with assistance from the treating surgeon, the Research Coordinator will update the REDCap Data Management System and the patient will be randomized electronically. To ensure that the number of subjects is about the same in the two arms of the study for each clinical site, the randomization scheme will assign patients in a 1:1 ratio in randomly permuted blocks of assignments stratified by clinical center. Block size will be determined randomly.

The patient will be the unit of randomization. If a patient has bilateral FIXIT eligible injuries, only one leg (the most severely injured leg) will be randomized to the study. The contralateral limb can be treated with either internal or external fixation methods at the discretion of the surgeon in consultation with the patient. The Research Coordinator will communicate the results of the randomization to the treating physician along with the exact date and time of the randomization. Enrollment and randomization results will be documented in the patient's chart according to center protocol.

5.5 Phase 4: Treatment and Baseline Data Collection

The date of injury is the 0 time for reckoning all follow-up visits (i.e. all follow-up visits are scheduled at specific times measured from the date of injury). The randomization computer program will generate a personalized appointment schedule for the patient; this schedule will indicate the ideal date for each follow-up visit, as well as the time window around the ideal date during which the follow-up visit may be done. It should be noted that in some cases, definitive surgery will occur after the patient is discharged from the hospital for initial treatment of their injury. Definitive fixation will not be considered a "readmission" based on established criteria evaluating outcomes. Furthermore, the first follow-up visit (at 6 weeks) may occur when the patient is still in the hospital.

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5.5.1. Treatment Arm Cross Over. Cross over from one treatment arm to another will be relatively rare. Patients who begin treatment with a ring fixator will be unlikely to switch to a tibial nail or plate. Surgeons believe that conversion from external fixation (with pins potentially tracking bacteria into the intramedullary canal) to a tibial nail after many weeks is associated with high infection rates [41], so this conversion will be unlikely. There is, however, the possibility that when some patients treated with a nail become infected, that the surgeon and patient may decide to have the nail removed and then converted to a external fixator to complete the treatment. If this occurs, the choice of using a standard (non-ring) fixator versus a modern ring fixator will be left to the discretion of the surgeon. These patients will be analyzed in their original nail treatment group on an intention to treat basis.

5.5.2. Baseline Data Collection. After patients are consented, the information listed below will be collected and entered into the REDCap Data Entry System. Details as to the information collected under each of these categories is included as Appendix 9.2.

Information to be collected at Baseline:

- Patient characteristics at the time of the injury
- Medical history and pre-existing co-morbidities
- General injury characteristics
- Study Injury characteristics
- Characteristics of the index hospitalization
- Surgical treatment delivered during the index hospitalization
- Characteristics of the definitive fixation
- Systemic and limb specific complications occurring during the initial hospitalization and the hospitalization during which the definitive fixation is performed

5.6. Phase 5: Post-Treatment Follow-up and Prospective Monitoring of Hospitalizations and Same Day Surgeries

Participants will return for follow-up visits at 6 weeks, 3, 6 and 12 months after injury. All participants will complete a telephone interview 18 and 24 months following injury. Participants who are not healed at 12 months will be asked to return for a brief exam and x-ray 18 months following injury. Participants not healed at 18 months will be asked to return for a brief exam and x-ray 24 months following injury. Participants will be considered healed if the treating surgeon indicates that the fracture is radiographically and clinically healed on study case report forms. Participants returning for clinic visits at 18 and/or 24 months will complete the interview during the visit.

Visit Windows

Each visit will have an interval of time surrounding the ideal date for the visit during which the visit may be done and the data included in the trial database. The ideal date for a visit is the exact anniversary from injury. Visit windows (+/- 2 weeks for all visits) will be constructed to be contiguous, so that at any point in time, some visit window is open, subject to a check on the minimum separation required between consecutive visits.

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These visits tend to mirror clinic visits per standard of care, however there may be some circumstances where patients are unwilling to return to the clinic. In these situations the Research Coordinator may obtain as much visit data as possible by phone and/or medical record review to prevent loss of important study information.

The types of specific data to be collected at each of the follow-up visits are listed below. Details as to the information collected under each of these categories are included as Appendix 9.2.

Information to be collected at follow-up:

- Clinical examination to include:
  - Review of all hospitalizations and same day surgeries since last follow-up
  - Assessment of complications
  - Assessment of fracture healing
  - Assessment of limb status and limb function
- Patient (or proxy) interview to assess:
  - Selected items pertaining to functional status and quality of life
  - Use of health services, including re-hospitalizations and same day surgeries at home institution or other health care facility

In addition to the scheduled follow-ups, all hospital admissions to the home institution and same day surgeries performed at the home institution related to the study fracture will be prospectively tracked by the research coordinator. Although protocols might vary from center to center, it is expected that research coordinators will routinely scan hospital admission and orthopaedic surgery logs to identify all admissions and same day surgeries of patients actively enrolled in METRC. When an admission or same day surgery is identified, information pertaining to that hospitalization or same day surgery will be collected.

A cumulative list of all admissions and same day surgeries (by date and facility) will be provided to the surgeon who is examining the patient at each follow-up. This information will be used to determine if any other admission or same day surgery (to the home institution or other health care facility) occurred since the last follow-up. If so, dates and reasons for the hospitalization/same day surgery together with the name and health care facility will be obtained. If the event occurred in a health care facility other than the home institution, written permission to access the relevant records from that facility will be obtained from the patient. Relevant information on each additional hospitalization or same day surgery will be obtained by the research coordinator within three weeks following the scheduled follow-up visit.

5.7. Primary and Secondary Outcomes

All outcomes will be assessed using widely used, standardized measures. They are described below.

5.7.1 Primary Outcome: Re-hospitalization for Complication. A hospital re-admission for a complication is defined as any re-admission to the hospital secondary to the treatment of the open tibia

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fracture for a defined set of complications. The list of complications includes: amputation (at any level), infection (defined using CDC criteria as described below), flap failure, non-union, mal-union, loss of reduction, or hardware failure. A similar definition has successfully been used by the core centers in previous published prospective studies and is consistent with the data used to generate the study power estimate [1].

5.7.2 Secondary Outcomes: Infection. Infection is defined as either deep or superficial. The presence of tibia infection will be defined by the criteria of the Centers for Disease Control (CDC) [42,43,44]. Whereas the occurrence of infection within 30 days after the operative procedure is a criteria specified by the CDC, infection in this protocol will include deep or superficial infections experienced at any time during study follow up. Deep infections are further defined as those that require operative treatment. Superficial infections are defined as those that are treated only with local antibiotics and wound care, and no operative treatment for the infection. The presence or history of infection will be assessed at every clinic visit as well as at every hospital re-admission or outpatient surgical procedure.

5.7.3 Secondary Outcomes: Fracture Healing. Fractures will be evaluated with standard 2 view radiographs of the tibia as is currently performed in standard practice at every clinic visit after the 2 week follow-up. Fracture healing is measured by the treating surgeon using standardized criteria as detailed in the clinic follow-up form.

5.7.4 Secondary Outcomes: Limb Function. Limb function will be measured using standard clinical assessments to include:

- Weight bearing and ambulation status (including use of aids): Weight bearing status will be assessed by the treating surgeon using standard classifications (full, partial, toe-touch, or non weight bearing). Ambulatory support devices may include canes, crutches, or walkers.

- Range of motion: Knee (flexion) and ankle (dorsiflexion and plantarflexion) joints will be measured using standard goniometric technique [45]

- Self selected walking speed: Subjects will be asked to walk 30 feet on a level surface, as fast as they can, with or without an assistive device. Use of assistive devices will be recorded, as described above. The time it takes for subjects to complete the task is measured with a stop watch and recorded as feet per second (ft/sec). Use of a stopwatch has been found to have excellent concurrent validity with the gold standard of infrared timing gates, with an inter-rater reliability of 0.99 for tests of walking speed [46]. Four feet per second is considered an appropriate cut-off for impaired speed, since 4.2 ft/sec is an approximate gait velocity for adults, 20-59 years old [47].

5.7.5 Secondary Outcomes: **Patient** Reported **Outcome and Quality of Life.** Outcomes from the patients' perspective will be assessed using standardized questionnaires:

The Veterans RAND Health Survey (VR-12 V1.0) The Veterans RAND 12 Item Health Survey (VR-12). The VR-12 is included as a generic health status measure from which a VR-6D can be computed for the purpose of a cost-utility analysis. The VR-12 is a multipurpose, self-administered generic measure of health status. It was developed to measure health-related quality of life, estimate disease burden and

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compare disease-specific benchmarks across populations. The VR-12 items measure eight health domains: general health perceptions; physical functioning; role limitations due to physical and emotional problems; bodily pain; energy-fatigue, social functioning and mental health . The instrument produces a physical health and mental health summary measure.

- **The Short Musculoskeletal Function Assessment (SMFA)** will be administered to patients 6, 12, 18, and 24 months following injury. 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 includes 34 items for assessing patient function. Subscores for the following 4 domains can be calculated: Daily Activities; Arm and Hand Function; Mobility and Emotional Status. 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. This scale has been chosen because it is a short, reliable, patient reported assessment of functional status that has been specifically designed for and validated in patients with musculoskeletal conditions, including acute injury [49].

- **Return to Usual Major Activity.** Return to Usual Major Activity (RUMA) will be assessed by asking patients what they were doing most of the time during the week before the interview. If the patient is working or going to school, s/he will be asked when s/he started work or school (relative to their injury). If the patient was on active duty at the time of the injury, questions specific to the military status will be included in the RUMA assessment.

- **The Paffenbarger Activity Scale** is being used to measure extent of physical activity before and 12 months after the injury. At baseline and at 12, 18 and 24 month follow-up, patients are asked to report the frequency and duration of their participation in physical activities, recreation or sport in the past week. The activities are then classified according to low, medium and high intensity activities and assigned levels of energy expenditure based on published guidelines (ref a). Total physical activity, expressed in kilocalories expenditure per week can be calculated. [50]

- **Depressive Symptoms.** The presence of depressive symptoms will be measured using the nine item depression scale of the Patient Health Questionnaire (PHQ-9) [51]. The PHQ-9 is a well validated tool for assisting clinicians in diagnosing depression. There are two components of the PHQ-9: (1) assessing symptoms and functional impairment to make a tentative depression diagnosis, and (2) deriving a severity score. The PHQ-9 is based directly on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV).

- **Post Traumatic Stress (PTSD).** PTSD will be measured using the standard PTSD Checklist (PCL), a 17-item measure that elicits responses for each of the DSM-IV disorders that comprise the diagnostic criteria for PTSD (intrusive, avoidant, and arousal symptoms). The psychometric properties of the PCL have been well established and it is the most widely used measure of PTSD.

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5.7.6 Secondary Outcome: Pain. Pain will be measured using the following measures:

- **Pain Intensity:** Overall Study limb as well as knee and ankle specific pain intensity will be measured using the 0-10 visual analogue scale used in the Brief Pain Inventory (see below). Pain intensity will be measured both at rest and during ambulation. The BPI pain intensity domain is compatible with the IMMPACT guidelines for assessing pain in clinical trials and the FDA Guidance for Industry on the use of Patient-Reported Outcome Measures [52].

- **The Brief Pain Inventory (BPI)** will be administered to patients at 6, 12, 18 and 24 months following injury. The BPI is a widely used, 15-item measure of pain intensity and interference with daily life [53]. The questionnaire assesses three key pain domains: pain intensity, pain interference, and efficacy of pain treatments or medications. It has been extensively validated in both English and Spanish.

- **Type and frequency of pain medication:** At each clinical follow up, the treating surgeon will record the type (grouped as acetaminophen, opioids, GABA analogues (like Neurontin or Lyrica), and NSAIDs (like Ibuprofen or Naproxen), and other) and frequency of pain medication use.

5.8 Other Outcomes

5.8.1 Satisfaction with Treatment: Patient satisfaction with treatment will be measured using the Short Form Patient Satisfaction Questionnaire (PSQ-18) at 12, 18 and 24 months following injury. The PSQ was originally developed by Ware and colleagues, included 80 items, and was successfully used as part of the RAND Health Insurance Experiment and Medical Outcomes Study [54]. The PSQ-18 measures all six sub-domains (technical quality, interpersonal manner, communication, financial aspects of care, time spent with doctor, and accessibility) as the longer form, as well as a single global satisfaction domain (ref: The Patient Satisfaction Questionnaire Short-Form (PSQ-18). [55] The domains measured by the PSQ-18 correlate at 0.8 or better with domains measured using the long form PSQ. The PSQ will be revised to be made specific to the treatments under study. Two questions specific to orthopaedic trauma care using the same format and structure as the rest of the instrument will be added to measure satisfaction with treatment for this study.

5.8.2 Health Care Costs. Costs for the initial hospitalization and subsequent care (within two years) will be derived using standard approaches used in all METRC studies. We will collect data on: length of hospital and ICU stay, number and types of surgeries performed during the initial acute hospitalization, hospital charges at the revenue center/cost department (UB92 hospital bills) and number of re-hospitalizations (including length of stay and charges). Costs will be calculated from charges at the revenue center/cost department line level using cost-to-charge ratios (CCRs) computed from the Medicare Cost Reports (MCRs) specific to the hospital and fiscal year of the hospital stay. We will also collect self reported utilization data on number of outpatient visits for medical care as well as indirect

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costs associated with informal caregiver time spent taking care of the participant. These data will be used to estimate total costs associated with care in both treatment groups.

5.9. Safety issues

Safety issues can be divided into (i) safety concerns related to the therapeutic interventions and (ii) concerns related to patient privacy.

5.9.1. Safety concerns related to the therapeutic interventions

As indicated above, there are no potential adverse effects specific to the use of a modern ring fixator compared to the use of a nail or plate. There are, however, several potential adverse effects common to all known treatments of severe open tibia shaft fractures. Most of these adverse effects are being examined as specific outcomes in the proposed study (i.e. infection, flap failure, amputation, non-union, malunion, loss of reduction or hardware failure). Other potential adverse effects include:

- An adverse reaction, side effect, occurrence of toxicity, or sensitive reaction in excess of expectations;
- Pulmonary embolism;
- Death

5.9.2. Safety issues related to patient privacy

It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient's anonymity be maintained in their data submission to the Data Coordinating Center. Patients will be identified only by an identification code but not by their name, SSN, or hospital medical record number. Study Site Investigators will maintain a separate confidential enrollment log which matches identifying codes with the patients' names and addresses (i.e., available only to local clinic staff). All study material will be maintained in strict confidence.

5.10. Retention

The study participants will receive an honorarium in recognition of their time and effort. A $33 payment will be given for completing each of the first 3 follow-up visits at 6 weeks, 3 months and 6 months; $50 will be given for completing each the 12, 18, and 24 month follow up. . (a total of $250 per patient for completing all 6 follow-ups) . We will also keep participants engaged through use of study updates on the METRC website and distribution of follow-up reminders and meaningful trinkets imprinted with the study logo.

5.11. Management of concomitant conditions

Concomitant conditions will be managed with the standards of care at the local treatment facility and should not be affected by study participation.

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5.12. Food and Drug Administration

Both methods of fixation have been approved by the FDA for the treatment of open tibia fractures.

5.13. Adverse event reporting

The FIXIT trial will monitor and report adverse events to ensure patient safety. Definitions and procedures for reporting adverse events are designed to satisfy 45 CFR Part 46, Subpart A; the "Common Rule", shared by 17 Departments and Agencies as well as 21 CFR 312, the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head. The FDA regulation requires notification of the FDA and participating investigators of any adverse event associated with the use of a test article that is "both serious and unexpected."

5.13.1. Definitions. We will use the following definitions in identifying adverse events.

- **Adverse event**. An adverse event is any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, device or clinical procedure and which may or may not have a causal relationship with the treatment. Adverse events include any unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants. The term "unanticipated problem" includes both new risks and increased rates of anticipated problems.

- **Serious adverse event**. A serious adverse event (SAE) is an adverse event occurring at any time during the study that results in death, life-threatening adverse drug or device experience, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant disability/incapacity. Other events may also be considered an SAE if, based on medical judgment, the event jeopardized the patient to the point of requiring medical or surgical intervention to prevent the occurrence of any of the conditions for an SAE listed above.

- **Unexpected adverse event**. An unexpected adverse event is any adverse event with specificity or severity that is not consistent with the risk information in the study protocol, current investigator brochure, or current package insert.

- **Associated with the use of the treatment** means that there is a reasonable possibility that the adverse experience may have been caused by the treatment.

- **5.13.2. Monitoring and Reporting adverse events.** Adverse events will be recorded on study data forms whether or not they are thought to be associated with the study or with one of the study treatments. Adverse events may be discovered during regularly scheduled visits or through unscheduled patient contacts between visits. As described above in Section 9.2, adverse events will be monitored both as secondary outcomes of the study (i.e. infection, flap failure,

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amputation, non-union, malunion, loss of reduction or hardware failure) as well as adverse events that are not outcomes per se of the study. These include

- An adverse reaction, side effect, occurrence of toxicity, or sensitive reaction in excess of expectations;
- Pulmonary embolism;
- Death

At its first meeting the DSMB will review definition of all outcomes, adverse events and serious adverse events and revisions to the protocol 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.

Where applicable, signs and symptoms associated with the adverse event will be graded as to severity by the clinical site staff as mild, moderate, or severe using the Common Terminology Criteria for Adverse Events.

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 each of the study centers. Analyses or listings of adverse events will not be provided to the IRBs; however, adverse events involving unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants must be reported to local IRBs as soon as possible after they are discovered. Each participating center is responsible for ensuring that all local IRB requirements for reporting adverse events are met.

5.13.3. Reporting serious adverse events. Serious adverse events (SAE) must be reported upon discovery at the clinical center. This will involve completing an SAE CRF describing the severity and details of the event. The SAE form, together with a memo summarizing the circumstances of the event and the current status of the patient, must be faxed to the Data Coordinating Center and to the DOD project officer within one working day of the discovery of the SAE. Also within one day, the clinical center must notify the DOD and Data Coordinating Center of the SAE by telephone or confirmed e-mail. The DOD project officer will work with the Data Coordinating Center to transmit the SAE form and memo to all study centers and to the DSMB.

A serious adverse event is defined as any adverse event as described above.

The DSMB will review each SAE report and provide comments to the DOD project officer within one week of receipt of the report. If requested by any member of the DSMB, a teleconference will be scheduled to discuss the SAE and recommend any actions to the DOD sponsor.

The clinical center must submit to the DOD project officer and to the Data Coordinating Center a follow-up memo within one month of the SAE (and periodic updates if needed) to report the details of the disposition of the SAE. The DOD project officer will work with the Data Coordinating Center to distribute the follow-up memo to the clinical center and to the DSMB.

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6. Statistical Design and Analysis

6.1. Study Aims and Hypotheses

Primary Aim: To compare the outcomes associated with modern ring external fixators versus standard internal fixation techniques in treating "severe" open tibia shaft or metaphyseal fractures with or without a bone defect of any size).

Primary Hypothesis: Among patients with open tibia shaft or metaphyseal fractures (with or without a bone defect of any size), the rate of re-hospitalization for complication will be lower for patients treated with ring fixators than those treated with standard internal fixation.

Secondary Hypotheses*:* Among patients with open tibia shaft or metaphyseal fractures (with or without a bone defect of any size), the overall rate of infections will be lower for patients treated with ring fixators than those treated with standard internal fixation. Measures of fracture healing, limb function, and patient reported outcomes (including pain) will be as good or better among patients treated with ring fixators than those treated with standard internal fixation.

Secondary Aim #1: To determine the percentage of Gustilo IIIB open tibia shaft fractures that can be treated successfully (i.e. adequately healed) without a soft tissue flap secondary to the use of ring external fixators.

Secondary Aim #2: To determine the one-year treatment costs associated with fixation of "severe" open tibia shaft or metaphyseal fractures using modern ring external fixators versus standard internal fixation techniques.

Secondary Aim #3: To determine patient reported levels of satisfaction with the fixation method and overall treatment and to compare satisfaction between the two treatment groups.

6.2. Outcome measures

The outcomes are defined above in Section 5.7. They are summarized below:

Primary Outcome Measure:
Hospital re-admission for one or more defined complications (i.e. infection, flap failure, amputation, non-union, malunion, loss of reduction or hardware failure)

Secondary Outcome Measures:

- Any infection, deep or superficial (CDC definitions)
- Fracture healing
- Limb Status and function
    - Weight bearing and ambulation status (including use of aids)
    - Range of motion of knee and ankle joints (active ROM only)
    - Self selected walking speed

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- Pain
    - VAS Pain Intensity
    - Use of pain medications
    - Brief Pain Inventory (BPI)
- Patient reported measures of function and quality of life
    - Overall measures (SF-12 and the SMFA)
    - Return to usual major activity (RUMA)
    - Activity level in sports and recreation (the Paffenbarger Activity Scale)
    - Depression (PHQ)
    - Post-traumatic stress (PCL Checklist)

Other Outcomes:

- Satisfaction with treatment (overall and specific to method of fixation)
- Cost of treatment (initial acute care treatment and one-year treatment costs)

6.3. Statistical analysis

The study design is a prospective, randomized controlled trial of modern external ring fixators vs. internal fixation in "severe" open tibia fractures that are most similar to war injuries. Randomization will be stratified by site). To address concerns regarding low participation/consent rates, we also include an observational arm, as has been done in other trials where randomization is difficult due to patient preferences. Main study outcomes will be evaluated at 1 year post-surgery.. Statistical analyses will follow the intent-to-treat paradigm, which means all patients will be analyzed according to the treatment group to which they were randomized.

For both binary and continuous outcomes, regression modeling may be employed if concerns about confounding arise, due to imbalances between treatment groups with respect to key prognostic baseline covariates. Random effects regression modeling may also be employed if concerns regarding the clustering of outcomes within centers emerge. As-treated analyses may also be conducted if there are issues with treatment crossovers.

Data collected 12-24 months following injury will be used to examine longer term outcomes of treatment for these patients.

6.4. Missing data

Missing data is a serious concern that complicates the interpretation of the study results. We will address this issue from both a trial conduct and analysis perspective. Regarding trial conduct, we will

1. Limit participant burden and inconvenience in data collection
2. Provide compensation for participation and completion in the study
3. Select high quality investigators
4. Provide pre-study training of investigators as well as on-study reinforcement
5. Reimburse investigators based on follow-ups completed rather than on per-patient basis.
6. Monitor and report missing data rates during the trial

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7. Emphasize the importance of full participation in the trial during the consent process.
8. Collect information on the reasons for missing data.
9. Actively engage participants in the study and educate them about the importance of their engagement.
10. Collect surrogate information on participants who miss clinic visits.
11. Hold regular METRC FIXIT meetings to discuss strategies for enrollment and engagement of participation
12. Set targets for acceptable rates of missing data and terminating sites that do not meet these targets.

While these efforts will help to minimize missing data, we recognize that missing data is inevitable.

With this in mind, we will conduct sensitivity analyses to evaluate the robustness of the trial results to various untestable assumptions about the missing data mechanism. In addition to unadjusted analyses, which rely on the missing completely at random assumption (testable), we will also estimate treatment effects (utilizing relevant auxiliary information) under the missing at random assumption. Further, we will explore the effect of departures from the missing at random assumption using pattern-mixture and selection modeling techniques.

6.5. Justification of sample size

The study will be powered for a RCT of treatments, although we will also follow patients who agree to participate in the follow-up assessments but refuse to be randomized.

Justification of Sample Size in the Randomized Study: We based the sample size on a two-group comparison of proportion of re-hospitalization for complications by 1 year. We assumed that the proportion of re-hospitalization in the internal fixation arm would be 60%. Using a two-sided 0.05 level test of the null hypothesis of no treatment difference, we need 140 patients to have 90% power to detect a 20% absolute reduction (35% relative reduction) in the proportion of re-hospitalization for the ring fixator arm. We will need 107 patients per arm to have 80% power to detect the same difference in outcome. With one interim analysis using an O'Brien-Fleming boundary, the number of patients must be inflated by 1% in order to preserve the overall type I error. Accounting for 10% missing data, we arrive at our proposed sample size of 156 per arm (based on 90% power) and 119 per arm (based on 80% power).

With 156 patients per arm, the power to detect differences in selected secondary outcomes of importance is summarized below.

Infection: Regarding the infection endpoint, the proposed sample size (assuming 10% missing data) yields 80% power to detect a difference between infection probabilities at 1 year of 28.6% (see LEAP study) vs. 14.3% for the internal and external fixation arms, respectively. This represents a 50% relative reduction in infection rates.

Pain: The proposed sample size (assuming 10% missing data) yields 80% power to detect a 7.5 point improvement in pain intensity, assuming the mean dysfunction in the internal fixation arm is 37.5 and a

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common standard deviation of 22.5. This translates into an effect size of 0.33, which is considered to be of small-medium magnitude.

Functional Outcome: The proposed sample size (assuming 10% missing data) yields 80% power to detect a 5.4 point improvement in dysfunction, assuming the mean dysfunction in the internal fixation arm is 30 and a common standard deviation of 16 (47). This translates into an effect size of 0.33, which is considered to be of small-medium magnitude.

Flap Coverage: This endpoint is relevant for type III-B fractures (approximately half the randomized population). Patients with type III-B fractures who receive internal fixation arm will require flap coverage. It is anticipated that ring fixation may obviate the need for flap coverage in some type III-B fracture patients. A secondary goal of the study is test the null hypothesis that the true flap coverage rate for type III-B fracture patients receiving ring fixation is less than or equal to 5% vs. the alternative that it is greater than 5%. The proposed sample size of 78 type III-B patients randomized to ring fixation (assuming 10% missing data) will, in repeated sampling, lead to rejection of null 76% of time if the true flap coverage rate is 15%.

Sample Size in the Observational Study: Guided by previous trials such as SPORT, we assume that 50% of patients who consent to participate will also agree to also participate in the randomized trial. Those who do not agree will be enrolled in the observation arm of the study. Thus, we anticipate enrolling approximately 312 patients into this arm.

6.6. Interim analysis

An independent Data and Safety Monitoring Board (DSMB), appointed by DOD, is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy. The DSMB is a multidisciplinary group with a written charge provided by METRC and DOD. The DSMB will meet in person to review the protocol. After the trial commences, the DSMB meets twice a year to review data or other issues. The DSMB may request more frequent meetings if necessary to fulfill it charge. It may also request additional safety reports on a more frequent basis. For example, all serious adverse events (SAE) are reported to the DSMB for their consideration and recommendations as they occur.

The DSMB will review semi-annual reports by masked treatment groups of the primary and secondary outcomes as well as all adverse events that are not identified as outcomes per se.

One formal interim analysis for efficacy is planned after 50% of patients in the randomized study have reached at least one year of follow-up. O'Brien-Fleming statistical stopping guidelines for efficacy apply.

The DSMB also reviews the overall progress of the trial in terms of recruitment and data quality and makes a formal recommendation to the DOD at the end of each scheduled meeting as to whether the trial should continue unmodified, continue with protocol modifications, or be stopped.

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7. Human subjects issues

7.1. Overview

The study protocol, questionnaires, and consent forms will be submitted to each participating center's IRB. Sites that recruit patients will submit their recruitment materials to their IRB prior to use. A site may not initiate any patient contact about the FIXIT trial until the site has IRB approval for the trial. All study personnel must complete training in the Protection of Human Subjects per DOD guidelines. The proposed study anticipates recruiting a significant proportion of racial/ethnic minorities (African-Americans, Asian-Americans and Hispanics) as well as non-Hispanic white subjects.

7.2. Institutional Review board (IRB) approval

A site may not initiate patient activities in the FIXIT trial until the site has IRB approval for the trial. Consent forms must have IRB approval. Sites must provide the Coordinating Center with a copy of the initial IRB approval notice and subsequent renewals as well as copies of the IRB approved consent statements.

7.3. Informed consent

A prototype consent will be prepared for both the RCT as well as the observational study. Individual sites may add material but may not delete material thought to be necessary for informed consent. Clinical sites may reformat and reword information to conform to their local requirements. The patient must sign the consent to be eligible for the trial or the observational study. The consent form will describe the purpose of the trial (or observational study), the procedures to be followed, and the risks and benefits of participation. Copies of the signed consent forms will be given to the patient, and this fact will be documented in the patient's record.

7.4. Patient confidentiality

All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper ,records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the IRB, DOD, or DSMB. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual site IRB and DOD requirements for compliance with The Health Insurance Portability and Accountability Act (HIPPA).

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9. Appendices

9.1. Participating Centers

Florida Orthopaedic Institute
OrthoIndy/Methodist Hospital
Orthopaedic Associates of Michigan
University of Maryland, Shock Trauma Center
University of California, San Francisco
University of Mississippi Medical Center
Denver Health and Hospital Authority
University of Texas, Southwestern Medical Center
Vanderbilt University Medical Center
Carolinas Medical Center
Boston Medical Center
Walter Reed National Medical Center
Naval Medical Center San Diego
Penna State University Hershey Medical Center
Duke University Hospital
University of Iowa Hospitals and Clinics
Wake Forest University Baptist Medical Center
MetroHealth Medical Center
Orlando Regional Medical Center
University of Texas Health Science Center, San Antonio
St. Louis University
University of Miami/Ryder Trauma Center
Hennepin County Medical Center/Regions Medical Center
University of Texas Health Science Center, Houston
Texas Tech University, Health Sciences Center at El Paso
Portsmouth Naval Medical Center
San Antonio Military Medical Center

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9.2. Data Collection Schedule

Assessment/Procedure	Base-line	6 wks	3 mo	6 mo	12 mo	18 mo	24 mo
Patient Consent	X						
Patient Characteristics							
Age, Gender, Race/Ethnicity	X						
Marital Status	X				X	X	X
Educational Level	X						
Usual Major Activity	X						
Current Military Service	X						
Branch of Military	X						
Highest Pay Grade while on active duty	X						
Income and Household Size	X						
Pre-Injury SF-12	X						
Pre-Injury Paffenbarger Activity Scale	X						
Smoking History	X				X	X	X
Self Efficacy	X						
Social Support	X						
Medical History and Co-morbidities							
Current medications	X						
Co-morbidities	X						
Insurance Coverage	X				X	X	X
Weight, Height	X				X	X	X
General Injury Characteristics							
Date and Time of Injury	X						
Mechanism of Injury	X						
Type of Injury (Blunt, Penetrating, Blast)	X						
Work Related (yes/no)	X						
Abbreviated Injury Scale (AIS) Scores	X						
OTA Classification for fractures	X						
Injury Severity Score (ISS)	X						
Glasgow Coma Scale (GCS) at Index Discharge	X						
FIXIT Injury Characteristics							
OTA and Gustilo Fracture Classifications	X						
Muscle Injury Characteristics	X						
Major Nerve Abnormalities	X						
Bone Loss Assessment	X						
Soft Tissue Injury Assessment	X						
Index Hospitalization							
Mode of Transport to Hospital (for cost)	X						
Transfer from Other Hospital	X						
Admission and Discharge Dates	X						

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Total ICU Length of Stay	X						
Discharge Disposition	X						
UB-92 Billing Data	X						
Assessment/Procedure	**Base-line**	**6 wks**	**3 mo**	**6 mo**	**12 mo**	**18 mo**	**24 mo**
Re-hospitalizations							
Type (acute, rehabilitation, LTC/SNF)	X	X	X	X	X	X	X
Surgical treatments performed	X	X	X	X	X	X	X
Relation to study injury and/or complications	X	X	X	X	X	X	X
Admission and Discharge Dates	X	X	X	X	X	X	X
Total ICU Length of Stay	X	X	X	X	X	X	X
Discharge Disposition	X	X	X	X	X	X	X
UB-92 Billing Data	X	X	X	X	X	X	X
Surgical Treatment							
Type, timing of all injury related surgeries	X	X	X	X	X	X	X
Definitive Fixation Timing and Characteristics	X	X	X	X	X		
Soft Tissue Coverage Timing & Characteristics	X	X	X	X	X		
Bone Grafting Timing and Characteristics	X	X	X	X	X		
Complications							
Limb Complications	X	X	X	X	X	X	X
Systemic Complications	X	X	X	X	X	X	X
Limb Status and Limb Function							
Leg Length Discrepancy	X				X	X	X
Rotational Alignment	X				X	X	X
Presence of Callus		X	X	X	X	X	X
Weight bearing & Ambulatory status		X	X	X	X	X	X
Fracture Healing (Radiographic Alignment)					X	X	X
Sensation	X				X	X	X
Pain Intensity		X	X	X	X	X	X
Type & dosage of pain medication		X	X	X	X	X	X
Range of Motion			X	X	X	X	X
Self Selected Walking Speed			X	X	X	X	X
Physical Therapy Need		X	X	X	X	X	X
Clinic Procedures Performed		X	X	X	X	X	X
Patient Reported Outcomes							
Brief Pain Inventory				X	X		X
Return to usual major activity/military service		X	X	X	X	X	X
VR-12		X	X	X	X	X	X
Short Musculoskeletal Function Assessment				X	X	X	X
Paffenbarger Activity Scale					X	X	X
Workers' Compensation/litigation status					X		

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Depression (PHQ)					X		X
PTSD (PCL)					X		X
Satisfaction with Care (PSQ-18)					X		X
Use of Health Care Resources (for cost)							
Ambulatory Care Visits (Number, Type)		X	X	X	X	X	X
Hours of Informal Care from Family / Friends		X	X	X	X	X	X
Billing Data							X

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Supplement 2

FIXIT:
Study Outcome Adjudication Process

Version 1
October 14, 2019
Revised December 23, 2019
Revised January 8, 2020

1. The Adjudication Panel and Their Charge

Three experienced orthopaedic trauma surgeons not affiliated with the current study will independently adjudicate the primary outcome. Due to the nature of the study interventions it is not possible to blind the reviewers to treatment or study site. Using METRC's distributed data system (REDCap), the reviewers will be presented a curated set of data from participant records. Reviewers will look at every operative case and readmission and verify whether complications should be counted as events based on criteria outlined below. For each of these complications, the panelists will be permitted to indicate that, based on the available data, they are unsure of their response. Further, they will be able to provide an opinion on whether the record needs further review by the panel and they may offer any additional comments in a narrative data field. The adjudicators will not interact with the original case report forms or the study sites in any way as part of the adjudication process.

2. Adjudication Criteria

Infection

- Differentiate between superficial (does not require operative treatment) vs. deep (requires operative treatment).
- Count cellulitis as a superficial infection.
- Only count superficial if it is treated with systemic antibiotics (IV or PO) for any duration of time.
- Count "surprise" positive cultures (e.g. cultures taken at time of non-union that is clinically not thought to be infected, but subsequently are positive). Separate these as "surprise positive" cultures so that sensitivity analysis can be performed
- Wound dehiscence/seroma/hematoma may or may not be an infection- will need to look at op note.
- Count pin tract infections if operatively treated

Amputation

- Has to be on the same limb as tibia fracture
- Can be any level; has to be related to the tibia fracture (consult op note)

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Non Union

- Don’t count planned bone grafts for bone defects.

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- If docking site breaks after ring is removed (or any procedure is done to promote healing after ring is removed), count as non-union
- If bone grafted before 2 months do not count it as a non-union even if it was not documented as a planned procedure.
- If you promote healing of the regenerate with surgery it is a non-union surgery
- "Planned" bone grafting at the docking site at time of "docking" at a does not count as non-union. However procedures to promote union later (e.g after 2 months from docking time) do count as non-union.

Flap Failure (i.e. soft tissue envelope/wound failure)

- Only counts if results in surgery. Mild superficial wound dehiscence treated in clinic with wet to dry etc. does not count.
- Count if flap dies and goes back to OR
- Count "skin failure" (i.e. skin develops necrosis and dehisces and there is no flap) goes back to OR
- Count seroma/hematoma (falls under skin failure)- could have a hematoma with and without wound dehiscence (count as one) goes back to OR
- If there is documented wound dehiscence and infection it's counted as infection

Hardware failure/loss of reduction

- Do not count hardware failure that does not lead to surgery.
- Count as an event if patient went back to OR and hardware changed (as long as it doesn't count as one of the other complications- i.e. don't want to double count)
- Count as an event if you have a ring and go back to OR and ring was adjusted (as long as it's not associated with another complications)

Malunion

- Only counts if the bone has healed (i.e. can't have a non-union and a malunion) and it results in surgery.

3. Initial Meeting

Prior to the start of the adjudication process, the principal investigator and the project director conduct an initial meeting with the adjudication team to describe the features and demonstrate the online adjudication tool. Study goals as well as the definition of the primary outcome are reviewed.

4. Adjudication Process

After each member reviews the first 20 cases, outcomes are checked for agreement among the raters. This process is repeated for subsequent batches of cases sent to the panel for review.

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Cases that do not indicate a unanimous vote on the outcome determination, as well as any records indicating that a panelist felt the record warrants further review, are reexamined by the panel as part of a follow up meeting. The panel members are provided additional details on the initial determination of each panel member and any notes provided in the narrative field of the assessment form are shared. Reviewers discuss the case and try to reach consensus at this time. Panel members are permitted to ask questions of the project director (non-clinician) about the data and may request additional data, if available, from the case report forms or through querying the site associated with a given record. If necessary, additional data or details are gathered by the project director and shared with the panel as part of another meeting if needed. Any questions of a clinical nature that cannot be answered by the project director can be discussed with the principal investigator. For specific cases or for follow up questions asked by the panel members, the panel may agree to forego a conference call meeting in favor of having the information shared by electronic mail.

In the event that unanimous agreement cannot be reached, majority rules will apply for outcome determination.

5. Role of Principal Investigator

In addition to participation in the initial meeting with the adjudicators, the principal investigator participates in the blinded review process of the records for the first 20 cases as a check for previously undetected problems with data quality and in order to answer questions raised as part of discussions about cases in need of additional review. In subsequent adjudication meetings, the principal investigator will be available to answer questions, should they arise. The principal investigator's assessment is not used in evaluating rater concordance nor is it revealed to the adjudicators at any time.

Prepared by:
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Approved by:
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Addendum December 23, 2019

As part of data cleaning and adjudication, members of the study team (O'Toole, study PI, Reider,MCC investigator, Huang, MCC Analyst) reviewed the following data to verify participant eligibility and injury classification:

- GA Type
- Soft tissue coverage
- OTA/OFC item related to vascular injury
- Diagnosis of infection dates

Since patients who are GA IIIC are not eligible for the study, we reviewed all participants with OTA/OFC artery injury and distal ischemia to make sure they are correctly classified and in facteligible.

Fractures that are initially treated with a flap should be classified as GA type IIIB, not IIIA. Theexception is special cases where the need for flap is obviated by a soft tissue reduction (e.g. shortening or rotating the fracture) to close the wound without a flap. All IIIB's that did not have a flap were reviewed to make sure they are correctly classified in keeping with these definitions.

Injuries classified as a IIIB typically have a flap before infection or wound dehiscence, not after.If the wound was closed consistent with a IIIA definition, and then later has a complication (infection or wound dehiscence) that requires a flap to treat the complication, the injury should be classified a IIIA with a complication, not a IIIB. All GA IIIB's with a flap date after a complication date were reviewed to make sure they were correctly classified.

IIIA fractures should not be initially treated with a flap, although they could have a flap later fora complication and be correctly classified as IIIA. We reviewed all IIIA's with flaps to make sure they were correctly classified.

Addendum January 8, 2020

Complications will be classified in the following manner:

1. Events for deep infection + soft tissue problem= will classify as BOTH
2. Events deep infection + non union= will classify as BOTH
3. Events for deep infection + amputation= will classify as BOTH
4. Events for non union + hardware failure= will classify as NON UNION

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Supplement 3

FIXIT: Statistical Analysis Plan for Main Outcome Paper (RCT Only) - Revision 1 *

March 28, 2020

The *first version of the* statistical analysis plan was finalized prior to first database lock.[1] Prior to *the first* database lock, the only analyses that were performed were (1) those masked to treatment group for purposes of DSMB reporting, and (2) a formal DSMB interim analysis conducted in April 2016. *Between the first database lock and the date of this revision, an analysis of the primary outcome (Section 8.2) and first secondary outcome (Section 8.3) was conducted for the purpose of submission of an abstract to OTA. With the exception of the data analyst, all study team members were masked to treatment assignment.*

1 CONSORT Diagram

The CONSORT Diagram will report the following items in sequential order: (1) the number screened patients, (2) the number of patients not enrolled and associated reasons, (3) the number of enrolled in RCT (4) in the RCT, the number randomized to the internal and external fixations arms (5) within treatment group, the number of late ineligibles, late refusals and administra- tive withdrawals and whether they received treatment, (6) within treatment group, number of cross-overs and not definitively fixed (7) within treatment group, number with follow-up greater than 365 days and percent of expected person-time of follow-up. Late ineligibles, late refusals and administrative withdrawals will be removed from all analyses. To the extent possible. the

*Revisions are marked by strikethroughs and by italic text.

[1] *The database was first locked on 1/15/20.*

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outcomes, complications, adverse events of late ineligibles, late refusals and administrative withdrawals who received treatment will be reported.

2 Follow-up Time

Patients were expected to return for study follow-up visits at 6 weeks, 3 months, 6 months and 12 months following date of injury. For patients with less than 365 days of follow-up, a medical review was conducted to document the last orthopaedic contact beyond the last study follow-up visit. Some patients consented to follow-up at 18 and 24 months.

Time zero will be date of randomization. Follow-up time will be defined as the minimum of death time, time of withdrawal, time of last orthopaedic contact or study visit and 365 days. A figure showing the distribution of follow-up time by treatment group will be produced. Differences between treatment groups will be evaluated by using Wilcoxon rank-sum test. Details of reasons for premature study discontinuation will be presented.

3 Pre-Injury Characteristics

A table will report summary statistics for characteristics of participants prior to their injuries by treatment groups. Pre-injury characteristics include age, gender, race-ethnicity, education, work status prior to injury, insurance, body mass index, tobacco use, poverty status and pre-injury VR-12.

4 Injury Characteristics

A table will report summary statistics for injury characteristics by treatment groups. Injury characteristics include open fracture type, wound length, bone loss assessment (smallest gap, largest gap, % of circumferential bone loss), tibial location (proximal, diaphyseal, distal), muscle loss, skin damage, arterial damage, contamination, and ISS.

5 Index Hospital Characteristics

A table will report summary statistics for index hospital characteristics by treatment groups. Index hospital characteristics include duration of hospital stay and transfer status; among those transferred, time between injury and

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index hospitalization as well as whether debridements were performed at non-index hospital.

6 Treatment Characteristics, Adherence to Treat-ment Protocol and Protocol Deviations

~~A table will report (1) the method of definitive fixation, (2) alignment onpost-operative films and (3) plan to treat bone defect, by treatment group.~~*All tables will focus on treatment characteristics, adherence to treatment protocol and protocol deviations within 365 days of randomization. A tablewill report the following treatment characteristics by group: (1) the methodof definitive fixation; (2) alignment on post-operative films, (3) plan to treat bone defect, (4) number of debridements for injury (not for a complication) prior to and including any performed on the day of definitive fixation, and (5) number with temporary internal fixation prior to definitive fixation. The table will also include the following adherence indicators by group:*[2] *(1) number of participants that did not get definitive treatment; (2) number of participants that did not receive the assigned definitive treatment (i.e., treatment crossovers); and (3) among participants who received their assigned treatment, the number that subsequently switched treatment after definitive fixation (e.g., number initially treated with internal fixation that later received a ring fixator; number initially treated with external ring fixation that later received internal fixation). Aside from treatment crossover, there are no other protocol deviations to report.*

For IIIB injuries, the proportion initially treated without a flap due to "soft tissue reduction" or similar techniques will be compared between treatment groups. Exact inferential techniques will be employed.

7 Serious Adverse Events and Complications Otherthan Outcomes

A table will report a summary of deaths, life-threatening or disabling events, and complications other than outcomes, stratified by treatment group.

[2]The study team will assist in adjudicating in treatment adherence. Adherence decisions will be documented.

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8 Outcome Analyses

8.1 Ascertainment

The primary way in which clinical outcome events are ascertained is through study follow-up visits and medical record reviews.

8.2 Primary Outcome

The primary outcome involves operative treatment of a major limb compli-cation during the index hospitalization, re-hospitalization for a major limb complication, or same day surgery for treatment of a major limb compli- cation. ~~Major limb complications include amputation, infection, soft tissue~~ ~~issue, non-union, malunion, loss of reduction and/or hardware failure.~~ *"Ma- jor limb complications" for the purpose of this study are defined to include amputation, infection, soft tissue issue, non-union, malunion, loss of reduc- tion and/or hardware failure.* All complications will be adjudicated by a three member panel of surgeons (see Adjudication SOP).

The treatment effect for the primary outcome will be reported two ways:

1. *(Primary)* Difference in the treatment-specific probability of at least one major limb complication during the index hospitalization, re-hospitalization for a major limb complication, or same day surgery for treatment of a major limb complication within 365 days of randomization. This difference will be estimated using survival analysis techniques, i.e., Kaplan-Meier.

2. Ratio of the treatment-specific average number of major limb complication events within 365 days of randomization. This ratio will be estimated using, possibly zero-inflated, Poisson or Negative Binomial regression with follow-up time as an offset. When counting events the following rules will apply:

   - Readmission for a complication plus k ($k > 0$) OR trips during the readmission for treatment of the complication= k events
   - Readmission for a complication with no OR trip= 1 event
   - Same day surgery (i.e. OR trip but no admission)= 1 event
   - k OR trips for major complications during index hospitalization = k events

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Analyses will be conducted based on modified intention-to-treat samples. 95% confidence intervals will be reported, with no adjustment for multiple comparisons.

8.3 Secondary Outcomes

A key secondary analysis will be similar to the primary outcome analysis, but will be specific to type of complication. That is, *for each of the six major limb complications,* we will report:

1. Difference in the treatment-specific probability of at least one major limb complication ~~of specific type~~ during the index hospitalization, re-hospitalization for a major limb complication ~~of specific type~~, or same day surgery for treatment of a major limb complication ~~of specific type~~ within 365 days of randomization. This difference will be estimated using survival analysis techniques, i.e., Kaplan-Meier.

2. Ratio of the treatment-specific average number of major limb complication events within 365 days of randomization. This ratio will be estimated using, possibly zero-inflated, Poisson or Negative Binomial regression with follow-up time as an offset. When counting events the following rules will apply:

    - Readmission for a complication of a specific type plus k ($k > 0$) OR trips during the readmission for treatment of the complication= k events
    - Readmission for a complication of a specific type with no OR trip= 1 event
    - Same day surgery for a complication of a specific type (i.e. OR trip but no admission)= 1 event
    - k OR trips for complication of a specific type during index hospitalization = k events

~~Other key secondary outcomes include (1) overall number of re-admissions events or same-day surgery events within 365 days of randomization, (2) number of re-admissions events or same-day surgery events within 365 days of randomization by type of event (not a major limb complication) (3) number of operatively and non-operatively treated pin-tract infections within 365 days of randomization, (4) number of non-operatively treated major limb complication within 365 days of randomization by complication type (i.e. infection; soft tissue problem; etc.), (5) number with a ring fixator on~~

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~~the limb within 365 days of randomization, (5) number healed within 365 days of randomization and (7) number of IIIB injuries treated without a flap due to soft tissue reduction within 365 days of randomization.~~

Other key secondary outcomes include:

3. *Ratio of the treatment-specific average number of OR trips during the index hospitalization, re-admission events or same-day surgery eventsfor any reason within 365 days of randomization. This ratio will be estimated using, possibly zero-inflated, Poisson or Negative Binomial regression with follow-up time as an offset. When counting events thefollowing rules will apply:*
    - *Readmission plus k (k > 0) OR trips during the readmission = k events*
    - *Readmission with no OR trip = 1 event*
    - *Same day surgery (i.e., OR trip but no admission)= 1 event*
    - *k OR trips during index hospitalization = k events*
4. *Ratio of the treatment-specific average number of surgeries related to the study injury (major limb complication + non-major limb compli-cation) within 365 days of randomization. This ratio will be estimatedusing, possibly zero-inflated, Poisson or Negative Binomial regressionwith follow-up time as an offset. When counting events the following rules will apply:*
    - *Readmission plus k (k > 0) OR trips during the readmission = k events*
    - *Readmission with no OR trip = 0 event*
    - *Same day surgery (i.e., OR trip but no admission)= 1 event*
    - *k OR trips during index hospitalization = k events*
5. *Difference in the treatment-specific probability of at least one oper- atively treated pin tract infection within 365 days of randomization. This difference will be estimated using survival analysis techniques, i.e., Kaplan-Meier;*
6. *Difference in the treatment-specific probability of at least one opera- tively or non-operatively treated pin tract infection within 365 days of randomization. This difference will be estimated using survival analy-sis techniques, i.e., Kaplan-Meier;*

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7. *Ratio of the treatment-specific average number of diagnosed pin tract infections within 365 days of randomization. This ratio will be esti- mated using, possibly zero-inflated, Poisson or Negative Binomial re- gression with follow-up time as an offset;*

8. *Ratio of the treatment-specific average number of diagnosed limb com-plications (of any type) that were non-operatively treated within 365 days of randomization by complication type (i.e., infection, soft tis-sue problem, etc.). This ratio will be estimated using, possibly zero- inflated, Poisson or Negative Binomial regression with follow-up time as an offset;*

9. *Among those who are not amputated, difference in the treatment-specificprobability of being in a ring fixator on the study limb at 365 days of randomization. This difference will be estimated using survival analy- sis techniques;*

10. *Among those who are not amputated, difference in the treatment-specificprobability of being healed within 365 days of randomization. This dif- ference will be estimated using survival analysis techniques.*

At a given assessment, a fracture will be considered healed if and only if the treating surgeon considered it healed. Healing is well-recognized as a subjective outcome. A more detailed evaluation of healing will be the subject of a future manuscript.

~~At a given assessment, a fracture will be considered healed if and only if~~

- ~~the treating surgeon considered it healed with a certainty rating of 9 or 10; or~~
- ~~RUST greater than equal to 10 or MRUST greater than or equal to 13.~~

~~We will assume that "once healed always healed". Sensitivity analyses will be conducted to evaluate different thresholds (certainty, RUST, MRUST) for healing. Depending on the structure of the data, interval censored data techniques may need to be employed.~~

Inference about Estimands (9) and (10) will be evaluated in the context of treatment differences with regards to amputation.

All analyses will be conducted based on modified intention-to-treat samples. 95% confidence intervals will be reported, with no adjustment for multiple comparisons.

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9 Subgroup Analysis

A subgroup analysis will be conducted with regards to the primary *and secondary* outcomes: Gustilo-Anderson open-fracture type IIIA and IIIB. An interaction test will be performed to evaluate if there is statistical evidence of differential subgroup effects within subgroup categories. Treatment effects within subgroups will be reported using the same approach described for the primary outcome.

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eTable 1. Additional Injury and Treatment Characteristics

	External (n = 122)	Internal (n = 132)
Wound Length, mean (SD), cm	14.9 (11.6)	11.1 (7.2)
Bone Loss Assessment		
Largest gap, mean (SD), cm	3.3 (3.7)	3.3 (3.6)
Smallest gap, mean (SD), cm	1.3 (2.8)	1.2 (2.3)
Circumferential bone loss, mean (SD), %	45.6 (38.0)	46.2 (40.4)
Muscle Damage, No. (%)		
None/minimal muscle in area	15 (12)	25 (19)
Muscle damaged but functional	82 (67)	72 (55)
Muscle damaged and not functional	25 (20)	35 (27)
Skin Damage, No. (%)		
Can be approximated	58 (48)	63 (48)
Cannot be approximated	30 (25)	35 (27)
Extensive degloving	34 (28)	34 (26)
Arterial Injury, No. (%)		
No injury	90 (74)	108 (82)
Artery injury without ischemia	32 (26)	23 (17)
Artery injury with distal ischemia	0 (0)	1 (1)
Contamination, No. (%)		
None or minimal contamination	22 (18)	30 (23)
Surface contamination	58 (48)	57 (43)
Imbedded in bone or deep soft tissues	42 (34)	45 (34)
Index hospitalization length of stay, mean (SD), days	19.0 (11.6)	19.1 (12.5)
Transferred from outside hospital, No. (%)	28 (23)	22 (17)
Internal Fixation Method, No. (%)	2 (2)	124 (94)
Plate	0 (0)	17 (13)
Intramedullary Nail	2 (2)	99 (75)
Both	0 (0)	8 (6)
External Fixation Method, No. (%)	117 (96)	4 (3)
Standard Ilizarov	31 (25)	2 (2)
Taylor spatial frame	78 (64)	1 (1)
Other	8 (7)	1 (1)
Varus/valgus malalignment, No. (%) [a]	28 (23)	21 (16)
Apex anterior/ posterior angulation, No. (%) [a]	23 (19)	16 (12)
Normal rotation alignment, No. (%) [a]	117 (96)	128 (97)
No Leg length discrepancy, No. (%) [a]	109 (89)	121 (92)
Type IIIB injures treated without a flap, No. (%)	1 (1)	(0)

[a] Alignment on post-operative films at time of definitive surgery.

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eTable 2. Average number of Major Limb Complications Treated with Surgery or Admission within 365 days of Randomization among Participants Treated with External versus Internal Fixation

	Zero Inflated Poisson Estimates, Mean (95% CI)		Treatment Effect	
	External (n = 122)	Internal (n = 132)	Incidence Rate Ratio	P Value
Major Limb Complication	1.66 (1.38, 2.00)	1.30 (1.02, 1.66)	1.28 (0.94, 1.74)	0.12
Amputation	0.16 (0.06, 0.40)	0.10 (0.05, 0.20)	1.55 (0.50, 4.83)	0.45
Infection	0.95 (0.72, 1.25)	0.72 (0.52, 1.00)	1.32 (0.86, 2.01)	0.20
Deep Infection	0.67 (0.47, 0.96)	0.71 (0.52, 0.98)	0.94 (0.58, 1.52)	0.81
Superficial Infection with Admission	0.05 (0.02, 0.11)	0	--[a]	--[a]
Pin Tract Infection with Admission	0.37 (0.25, 0.57)	0.01 (0, 0.06)	45.41 (6.13, 336.33)	< 0.001
Soft Tissue Problem	0.47 (0.30, 0.72)	0.48 (0.31, 0.72)	0.98 (0.54, 1.78)	0.95
Non-Union	0.30 (0.21, 0.43)	0.33 (0.24, 0.48)	0.90 (0.54, 1.48)	0.67
Malunion	0.01 (0.00, 0.06)	0	--[a]	--[a]
Hardware Failure/Loss of Reduction	0.20 (0.13, 0.30)	0.02 (0.01, 0.08)	8.02 (2.39, 26.88)	0.001

[a] Statistical analysis not conducted due to sparse data.

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eTable 3: Average number of Operating Room (OR) trips and Non-Operatively Treated Complications within 365 days of Randomization among Participants Treated with External versus Internal Fixation

Estimates (95% CI) within 365 days	Zero Inflated Poisson Estimates (95% CI)		Treatment Effect	
	External (n = 122)	**Internal (n = 132)**	**Incidence Rate Ratio**	**P Value**
OR trips or same day surgeries for any reason[a]	5.88 (5.46, 6.34)	4.84 (4.46, 5.24)	1.22 (1.13, 1.31)	< 0.001
Surgeries related to the study injury[a]	5.36 (4.95, 5.79)	4.37 (4.01, 4.75)	1.23 (1.13, 1.33)	< 0.001
Diagnosed pin tract infections	0.42 (0.32, 0.56)	0.02 (0.00, 0.07)	25.61 (6.22, 105.49)	< 0.001
Non-operatively treated major limb complications	0.30 (0.21, 0.43)	0.16 (0.10, 0.26)	1.82 (1.02, 3.24)	0.04
Non-operatively treated infection	0.26 (0.18, 0.38)	0.13 (0.08, 0.23)	1.94 (1.01, 3.72)	0.05
Non-operatively treated superficial infection	0.07 (0.03, 0.14)	0.12 (0.07, 0.21)	0.56 (0.23, 1.32)	0.19
Non-operatively treated pin tract infection	0.19 (0.12, 0.30)	0.01 (0.00, 0.06)	22.92 (3.06, 171.74)	0.003
Non-operatively treated soft tissue issue	0.03 (0.01, 0.08)	0.03 (0.01, 0.09)	0.78 (0.18, 3.50)	0.75
Non-operatively treated malunion	0.02 (0.00, 0.07)	0	[b]	[b]

[a] Poisson regression used.
[b] Statistical analysis not conducted due to sparse data.

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eTable 4: Operatively and Non-Operatively Treated Pin Tract Infections within 365 days of Randomization among Participants Treated with External versus Internal Fixation

	Kaplan-Meier Estimates (95% CI)		Treatment Effect		
	External (N = 122)	Internal (N = 132)	Risk Difference	Relative Risk	P Value
Operatively treated pin tract infection	16.3 (10.7, 24.3)	0.8 (0.1, 5.8)	15.4 (8.5, 22.2)	19.52 (2.66, 143.50)	0.004
Operatively or non-operatively treated pin tract infection	32.2 (24.6, 41.5)	1.6 (0.4, 6.3)	30.6 (21.6, 39.1)	20.04 (4.94, 81.29)	< 0.001

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eTable 5: Remaining in an External Fixator and Fracture Healing at 365 days of Randomization among Participants Treated with External versus Internal Fixation[a]

	Kaplan-Meier Estimates (95% CI)		Treatment Effect		
	External (N = 115)	**Internal (N = 120)**	**Risk Difference (%)**	**Relative Risk**	**P Value**
In a ring fixator on the study limb	35.6 (26.3, 44.4)	7.7 (3.2, 13.0)[b]	27.9 (16.8, 37.8)	4.60 (2.44, 12.20)	< 0.001
Being healed	49.0 (39.7, 59.3)	46.2 (36.6, 57.0)	2.8 (-11.4, 17.0)	1.06 (0.79, 1.43)	0.70
Interval censored estimates	59.7 (51.6, 68.0)	59.0 (50.4, 67.7)	0.8 (-11.2, 12.7)	1.01 (0.83, 1.24)	0.90

[a] Excludes patients who were amputated.
[b] **Patients were cross overs or switched to external fixation after receiving a nail**

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eTable 6. Major Limb Complications Treated with Surgery or Admission within 365 days of Randomization by "Severe" Type IIIA and Type IIIB Injuries

	Kaplan-Meir Estimates (95%CI)		Treatment Effect				
	External (N = 122)	Internal (N = 132)	Risk Difference	Relative Risk	P Value	Interaction Test 1: Diff. in risk difference p-value	Interaction Test 2: Ratio of relative risk p-value
Major Limb Complication							
"Severe" Type IIIA	53.9% (40.3%, 68.7%)	41.9% (28.3%, 58.7%)	12.0% (-9.4%, 32.3%)	1.29 (0.82, 2.03)	0.281	0.424	0.567
Type IIIB	67.4% (56.5%, 77.9%)	44.8% (34.9%, 56.0%)	22.6% (7.0%, 37.1%)	1.50 (1.13, 2.00)	0.006		
Amputation							
"Severe" Type IIIA	2.1% (0.3%, 13.9%)	5.3% (1.3%, 20.0%)	-3.2% (-11.5%, 5.1%)	0.39 (0.04, 4.19)	0.447	0.903	0.638
Type IIIB	6.8% (2.9%, 15.6%)	9.3% (4.8%, 17.7%)	-2.5% (-10.9%, 5.9%)	0.73 (0.25, 2.14)	0.568		
Infection							
"Severe" Type IIIA	34.4% (22.7%, 49.9%)	21.3% (11.7%, 37.1%)	13.1% (-5.6%, 30.9%)	1.62 (0.80, 3.27)	0.186	0.680	0.525
Type IIIB	41.6% (31.2%, 53.9%)	33.6% (24.5%, 44.9%)	8.1% (-7.3%, 23.1%)	1.24 (0.82, 1.87)	0.306		
Deep Infection							
"Severe" Type IIIA	17.3% (9.1%, 31.7%)	21.3% (11.7%, 37.1%)	-3.9% (-20.2%, 12.6%)	0.81 (0.34, 1.92)	0.642	0.843	0.758
Type IIIB	31.9% (22.4%, 44%)	33.6% (24.5%, 44.9%)	-1.7% (-16.4%, 13.1%)	0.95 (0.60, 1.49)	0.823		
Superficial Infection with Admission						[a]	[a]
"Severe" Type IIIA	4.2% (1.1%, 15.6%)	0		[a]	[a]		

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Type IIIB	5.8% (2.2%, 14.7%)	0	[a]	[a]	[a]		
Pin Tract Infection with Admission							
"Severe" Type IIIA	23.7% (13.9%, 38.7%)	0	[a]	[a]	[a]	[a]	[a]
Type IIIB	18.4% (11.1%, 29.5%)	1.2% (0.2%, 8.3%)	17.2% (7.7%, 26.3%)	15.06 (2.02, 112.33)	0.009		
Soft Tissue Problems							
"Severe" Type IIIA	14.9% (7.4%, 28.7%)	9.3% (3.6%, 22.8%)	5.6% (-7.8%, 18.8%)	1.61 (0.50, 5.12)	0.424	0.449	0.408
Type IIIB	22.1% (14.1%, 33.5%)	23.7% (16.0%, 34.3%)	-1.6% (-14.7%, 11.5%)	0.93 (0.52, 1.66)	0.808		
Non-Union							
"Severe" Type IIIA	17.5% (9.2%, 32%)	32.9% (20.1%, 50.7%)	-15.3% (-33.5%, 3.9%)	0.53 (0.24, 1.17)	0.122	0.069	0.070
Type IIIB	28.6% (19.5%, 40.8%)	22.1% (14.5%, 32.8%)	6.5% (-7.5%, 20.2%)	1.29 (0.75, 2.25)	0.363		
Malunion							
"Severe" Type IIIA	0	0	[a]	[a]	[a]	[a]	[a]
Type IIIB	1.4% (0.2%, 9.6%)	0	[a]	[a]	[a]		
Loss of Reduction and/or Hardware Failure							
"Severe" Type IIIA	25.7% (15.5%, 40.8%)	0	[a]	[a]	[a]	[a]	[a]
Type IIIB	11.1% (5.7%, 21.1%)	3.7% (1.2%, 11%)	7.5% (-0.9%, 15.8%)	3.02 (0.83, 10.97)	0.095		

[a] Statistical analysis not conducted due to sparse data.

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eTable 7. Average Number of Major Limb Complications Treated with Surgery or Admission by "Severe" Type IIIA and Type IIIB Injuries

	Zero Inflated Poisson Estimates (95% CI)		Treatment Effect			
	External (N = 122)	**Internal (N = 132)**	**Incidence Rate Ratio**	**P Value**	**Interaction Test 1: Diff. in ratio p-value**	**Interaction Test 2: Ratio of ratio p-value**
Major Limb Complication						
"Severe" Type IIIA	1.23 (0.88, 1.73)	0.99 (0.63, 1.54)	1.25 (0.71, 2.19)	0.440	0.845	0.847
Type IIIB	1.94 (1.56, 2.42)	1.46 (1.09, 1.94)	1.33 (0.93, 1.92)	0.122		
Amputation						
"Severe" Type IIIA	0.02 (0.00, 0.15)	0.05 (0.01, 0.22)	0.43 (0.04, 4.72)	0.490	0.242	0.247
Type IIIB	0.27 (0.10, 0.72)	0.13 (0.06, 0.26)	2.11 (0.61, 7.30)	0.241		
Infection (any)						
"Severe" Type IIIA	0.71 (0.44, 1.15)	0.58 (0.30, 1.15)	1.23 (0.54, 2.80)	0.630	0.786	0.792
Type IIIB	1.11 (0.79, 1.55)	0.79 (0.55, 1.14)	1.40 (0.85, 2.29)	0.187		
Deep Infection						
"Severe" Type IIIA	0.35 (0.17, 0.72)	0.58 (0.30, 1.15)	0.60 (0.22, 1.62)	0.312	0.217	0.266
Type IIIB	0.89 (0.59, 1.33)	0.78 (0.54, 1.12)	1.14 (0.66, 1.95)	0.647		
Superficial Infection with Admission						
"Severe" Type IIIA	0.04 (0.01, 0.17)	0	[a]	[a]	[a]	[a]
Type IIIB	0.06 (0.02, 0.15)	0	[a]	[a]		
Pin Tract Infection with Admission						

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"Severe" Type IIIA	0.47 (0.26, 0.87)	0	[a]	[a]	[a]	[a]
Type IIIB	0.31 (0.18, 0.54)	0.01 (0.00, 0.09)	25.42 (3.30, 195.50)	0.002		
Soft Tissue Issue						
"Severe" Type IIIA	0.48 (0.22, 1.05)	0.23 (0.08, 0.68)	2.07 (0.55, 7.79)	0.287	0.361	0.192
Type IIIB	0.46 (0.27, 0.76)	0.60 (0.38, 0.94)	0.77 (0.39, 1.51)	0.442		
Non-Union						
"Severe" Type IIIA	0.20 (0.1, 0.38)	0.33 (0.19, 0.57)	0.59 (0.25, 1.40)	0.235	0.250	0.258
Type IIIB	0.37 (0.24, 0.56)	0.34 (0.21, 0.54)	1.09 (0.58, 2.05)	0.781		
Malunion						
"Severe" Type IIIA	0	0	[a]	[a]	[a]	[a]
Type IIIB	0.01 (0.00, 0.10)	0	[a]	[a]		
Loss of Reduction and/or Hardware Failure						
"Severe" Type IIIA	0.26 (0.15, 0.46)	0	[a]	[a]	[a]	[a]
Type IIIB	0.16 (0.08, 0.33)	0.04 (0.01, 0.11)	4.35 (1.13, 16.75)	0.034		

[a] Statistical analysis not conducted due to sparse data.

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eTable 8. Average Number of Operating Room (OR) Trips and Non-Operatively Treated Complications within 365 Days of Randomization by "Severe" Type IIIA and Type IIIB Injuries

	Zero Inflated Poisson Estimates (95% CI)		Treatment Effect			
	External (N = 122)	Internal (N = 132)	Incidence Rate Ratio	P Value	Interaction Test 1: Diff. in ratio p-value	Interaction Test 2: Ratio of ratio p-value
OR Trips or Same Day Surgeries for any Reason[a]						
"Severe" Type IIIA	4.59 (4.01, 5.26)	3.39 (2.86, 4.01)	1.36 (1.1, 1.67)	0.005	0.350	0.330
Type IIIB	6.72 (6.14, 7.35)	5.53 (5.04, 6.06)	1.22 (1.12, 1.32)	< 0.001		
Surgeries Related to the Study Injury[a]						
"Severe" Type IIIA	4.03 (3.49, 4.65)	3.13 (2.62, 3.74)	1.29 (1.02, 1.61)	0.032	0.847	0.845
Type IIIB	6.22 (5.67, 6.83)	4.96 (4.50, 5.46)	1.26 (1.15, 1.37)	< 0.001		
Diagnosed Pin Tract Infections						
"Severe" Type IIIA	0.52 (0.34, 0.79)	0.03 (0.00, 0.18)	20.51 (2.76, 152.10)	0.004	0.811	0.806
Type IIIB	0.36 (0.24, 0.53)	0.01 (0.00, 0.09)	29.23 (3.96, 215.92)	0.001		
Non-operatively Treated Major Limb Complication						
"Severe" Type IIIA	0.26 (0.14, 0.47)	0.20 (0.09, 0.46)	1.28 (0.46, 3.54)	0.634	0.365	0.380
Type IIIB	0.33 (0.21, 0.51)	0.15 (0.08, 0.26)	2.24 (1.09, 4.59)	0.030		
Non-operatively Treated Infection						
"Severe" Type IIIA	0.26 (0.14, 0.47)	0.20 (0.09, 0.46)	1.28 (0.46, 3.54)	0.634	0.306	0.287
Type IIIB	0.26 (0.16, 0.42)	0.10 (0.05, 0.19)	2.63 (1.13, 6.14)	0.027		
Non-operatively Treated						

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Superficial Infection						
"Severe" Type IIIA	0	0.17 (0.08, 0.39)	[b]	[b]	[b]	[b]
Type IIIB	0.11 (0.06, 0.23)	0.10 (0.05, 0.19)	1.17 (0.44, 3.12)	0.755		
Non-operatively Treated Pin Tract Infection						
"Severe" Type IIIA	0.26 (0.14, 0.47)	0.03 (0.00, 0.18)	10.25 (1.32, 79.53)	0.028	[b]	[b]
Type IIIB	0.14 (0.07, 0.29)	0	[b]	[b]		
Non-operatively Treated Soft Tissue Issue						
"Severe" Type IIIA	0 (0.00)	0 (0.00)				
Type IIIB	0.04 (0.01, 0.13)	0.05 (0.02, 0.13)	0.88 (0.20, 3.92)	0.864	[b]	[b]
Non-operatively Treated Malunion						
"Severe" Type IIIA	0 (0.00)	0 (0.00)				
Type IIIB	0.03 (0.01, 0.11)	[b]	[b]	[b]		

[a] Poisson regression used.
[b] Statistical analysis not conducted due to sparse data.

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eTable 9. Operatively and Non-Operatively Treated Pin Tract Infections within 365 Days of Randomization by "Severe" Type IIIA and Type IIIB Injuries

			Treatment Effect				
	External (N = 122)	**Internal (N = 132)**	**Risk Difference**	**Relative Risk**	**P Value**	**Interaction Test 1: Diff. in risk difference p-value**	**Interaction Test 2: Ratio of relative risk p-value**
Operatively Treated Pin Tract Infection							
"Severe" Type IIIA	19.7% (10.7%, 34.4%)	0	[a]	[a]	[a]	[a]	[a]
Type IIIB	14.1% (7.8%, 24.7%)	1.2% (0.2%, 8.4%)	12.9% (4.3%, 21.2%)	11.43 (1.5, 87.11)	0.020		
Operatively or Non-operatively Treated Pin Tract Infection						0.307	0.820
"Severe" Type IIIA	38.7% (26.4%, 54.2%)	2.3% (0.3%, 15.4%)	36.4% (20.8%, 50.1%)	16.64 (2.32, 119.39)	0.006		
Type IIIB	28.1% (19.1%, 40.1%)	1.2% (0.2%, 8.3%)	26.8% (15.8%, 37.2%)	23.01 (3.17, 167.25)	0.002		

[a] Statistical analysis not conducted due to sparse data.

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eTable 10. Remaining in an External Fixator and Fracture Healing at 365 Days of Randomization by "Severe" Type IIIA and Type IIIB Injuries

			Treatment Effect				
	External (N = 115)	**Internal (N = 120)**	**Risk Difference**	**Relative Risk**	**P Value**	**Interaction Test 1: Diff. in Risk Difference p-value**	**Interaction Test 2: Ratio of Relative Risk p-value**
In a Ring Fixator on the Study Limb							
"Severe" Type IIIA	24.0% (12.8%, 37.0%)	1.9% 0%, 7%%)	22.1% (9.3%, 34.8%)	12.95 (2.83, Inf.)	<0.001	0.247	[a]
Type IIIB	44.2% (31.7%, 55.3%)	10.7% (4.0%, 17.8%)	33.5% (18.9%, 47.7%)	4.13 (2.16, 10.80)	< 0.001		
Being Healed							
"Severe" Type IIIA	50.5% (36.5%, 66.5%)	56.1% (39.5%, 74.0%)	-5.5% (-28.3%, 17.9%)	0.90 (0.58, 1.40)	0.647	0.423	0.409
interval censored	61.2% (48.8%, 73.7%)	68.0% (53.4%, 81.8%)	-6.8% (-25.7%, 12.5%)	0.90 (0.67, 1.21)	0.491	0.386	0.386
Type IIIB	47.8% (35.8%, 61.4%)	41.2% (30.0%, 54.6%)	6.6% (-11.4%, 24.1%)	1.16 (0.77, 1.74)	0.476		
interval censored	58.9% (48.3%, 69.9%)	54.8% (44.6%, 65.7%)	4.1% (-11.2%, 19.1%)	1.07 (0.82, 1.41)	0.603		

[a] Statistical analysis not conducted due to sparse data.