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

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Summary: The treatment of high-energy open tibia fractures is challenging in both the military and civilian environments. Treatment with modern ring external fixation may reduce complications common in these patients. However, no study has rigorously compared outcomes of modern ring external fixation with commonly used internal fixation approaches. The FIXIT study is a prospective, multicenter randomized trial comparing 1-year outcomes after treatment of severe open tibial shaft fractures with modern external ring fixation versus internal fixation among men and women of ages 18–64. The primary outcome is rehospitalization for major limb complications. Secondary outcomes include infection, fracture healing, limb function, and patient-reported outcomes including physical function and pain. One-year treatment costs and patient satisfaction will be compared between the 2 groups, and the percentage of Gustilo IIIB fractures that can be salvaged without soft tissue flap among patients receiving external fixation will be estimated.

Key Words: external ring fixation, internal fixation, open tibia fractures

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BACKGROUND AND RATIONALE

The treatment of high-energy open tibia fractures is challenging in both the military and civilian environments.[1–9] These injuries are commonly associated with hospital readmissions for complications which are often associated with poor long-term outcomes.[1] The Lower Extremity Assessment Project reported rehospitalization rates for complications after severe open tibia fractures as high as 57%; several other studies report rates of surgical site infection and osteomyelitis ranging from 14.3% to 60.0%.[1,4–7,10] Traditional treatment protocols use intramedullary nails or plates for fracture fixation which involves placing metal (the nail or plate) beneath the skin at the fracture site. Multiple studies demonstrate that infection rates tend to increase whenever hardware is placed within a wound, likely because of the difficulty the immune system has in clearing bacteria from the biofilm that develops on metallic surfaces.[11–13]

Treatment with modern ring external fixation, which does not place any hardware at the fracture site, may reduce infections and hospital readmissions. Two small retrospective case series conducted at US military centers showed a relatively low infection rate between 1.6% and 3.0% among patients with severe open tibia fractures treated with ring fixators.[4,5] In one civilian study, no infections were reported among severe open tibia fractures treated with ring fixators.[14] These figures are based on retrospective data but seem to present a lower estimate of infection rates than previously reported for similar injuries treated with internal fixation.[4,5,10]

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 used for limb lengthening and treatment of large bone defects using a process known as "distraction osteogenesis."[15–25] Advocates of this technique use it to treat large bone defects by creating an osteotomy 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. Similar techniques can also be used to perform "soft tissue" reductions resulting in closure of traumatic wounds that otherwise would need a flap.

Although there is a theoretical basis to support an advantage of external ring fixation and some promising clinical data, it is not yet clear that modern ring fixators will

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perform better than the current standard in a rigorous head-to-head trial. Several studies have investigated differences in outcomes comparing external with internal fixation, but they are limited in size and design. These studies included only small numbers of patients within a single center, some were retrospective case studies, and most did not include "severe" open fractures which are common in the military population and civilians with high-energy trauma (tibias that need a flap for limb salvage).[6,26–29] The use of older-model external fixators for high-energy trauma has historically been associated with poor outcomes such as malunion, and it remains to be proven whether newer ring fixators, which offer improved stability over older models, can overcome these problems.[30] It is possible that modern ring external fixators may reduce the deep infection rate but negatively impact other outcomes such as patient satisfaction and functional outcomes secondary to the long duration of time required for fracture healing with the frame in place. Furthermore, there are complications that are unique to ring fixators such as refracture of the bone after fixator removal and pin track infections that have an unknown effect on outcomes.

The purpose of this study was to compare 1-year outcomes after treatment of severe open tibia shaft fractures with external ring fixation versus internal fixation in a prospective, multicenter randomized controlled trial (RCT). It is hypothesized that compared with those treated with internal fixation: (1) the probability of rehospitalization for major limb complications will be lower for patients treated with modern ring external fixation; (2) the incidence of infection will be lower among patients treated with modern ring external fixation; (3) measures of fracture healing, limb function, and patient-reported outcomes including physical function, pain, and return to usual activities will not be worse (ie, noninferior) for patients receiving modern ring external fixation. The study is also designed to estimate the percentage of Gustilo IIIB open shaft fractures that can be salvaged without a soft tissue flap among patients receiving external fixation and to compare 1-year treatment costs and patient satisfaction between the 2 treatment groups.

METHODS: TRIAL DESIGN, PATIENT SELECTION

Overview of Trial Design and Randomization

The study was initiated at 24 US trauma centers participating in the Major Extremity Trauma Research Consortium (METRC).[31] The list of participating centers can be found in Appendix 1. The study protocol, including the written informed consent form, was approved by the Johns Hopkins Bloomberg School of Public Health (location of the METRC Coordinating Center), the DoD Human Subjects Research Protection Office (study sponsor), and the local Institutional Review Board at each participating center. Furthermore, each site was required to obtain DoD Human Subjects Research Protection Office approval of local Institutional Review Board documents as well as certification by the Coordinating Center to ensure proper training of all study personnel on study procedures and data collection before the initiation of the study.

The study population consists of patients ages 18–64 with a "severe" (Table 1) open tibia fracture suitable for limb salvage with either a modern ring external fixator or internal fixation (ie, intramedullary nail or plate). Eligible patients who provide informed consent are randomized to 1 of the 2 fixation techniques in permuted blocks stratified by clinical center and administered centrally by the Coordinating Center using REDCap,[32] the web-based, distributed data collection system used for all METRC studies. Block size varies by site based on anticipated site-specific study volume and over time; sites are unaware of the block size.

Patients are randomized before definitive fixation. In this study, there is no practical way to blind patients, surgeons, and research coordinators to treatment assignment. Eligible patients who refuse randomization are offered the opportunity to enroll in an observational (OBS) prospective

TABLE 1. Inclusion and Exclusion Criteria for the FIXIT Study

Inclusion Criteria	Exclusion Criteria
1. 18–64 yrs of age 2. "Severe" open tibia fractures (diaphyseal or metaphyseal; OTA 41, 42, or 43) which we define for this study as meeting at least 1 of the following criteria: a) Gustilo type IIIB (open fracture that would require a rotational or free flap if the limb were salvaged at its natural length)* b) Gustilo type IIIA where extensive contamination or muscle damage precludes nail/plate placement at first debridement and therefore requires serial debridements* c) Gustilo type IIIA where injury would have been classified as a IIIB, but because enough muscle was removed, the skin could be closed* d) Gustilo type IIIA where after debridement, the minimum distance between bones at the fracture site ("bone gap") is greater than 1 cm e) Gustilo type IIIA where fasciotomies were performed for impending or diagnosed compartment syndrome, and wounds could not be primarily closed*	1. Traumatic amputation of the study tibia 2. Definitive fixation of the study injury before study enrollment 3. Treatment for an infection of the study injury before enrollment 4. Non-English or non-Spanish speaking 5. Incarceration 6. Previous diagnosis of a severe psychiatric condition preventing follow-up 7. Intellectually challenged without adequate family support preventing follow-up 8. Residence outside the catchment area preventing follow-up 9. Non-ambulatory because of an associated complete spinal cord injury 10. Nonambulatory before the injury because of pre-existing condition 11. Complex ipsilateral pilon/plateau fracture. "Complex" pilons and plateaus were all pilons and plateaus except fractures with simple intra-articular fractures that involved the ankle or knee, simple ankle fractures, and Shatzker II tibial plateau fractures as these injuries are thought to have less impact on the overall outcomes.

*The fractures in these groups can have a bone gap of any size (including no gap) after debridement.

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cohort study. The OBS study is included to address concerns about patients' willingness to be randomized and to evaluate the generalizability of the RCT results. Treatment for these OBS study patients is based on patients' preference. To limit potential for selection bias, patients enrolled in the OBS arm must meet all eligibility requirements for the RCT. Specifically, patients who have already had definitive fixation (eg, a intramedullary nail on the night of injury before study screening for the OBS study) are not eligible for the OBS arm. All enrolled patients are followed for 12 months after the date of injury.

Patient Selection

Eligible for inclusion in the study are adult patients who are treated for an open diaphyseal or metaphyseal tibia fracture meeting one or more of the injury criteria listed in Table 1. These criteria include all Gustilo type IIIB tibia fractures and a select group of "severe" type IIIA fractures. Patients are not excluded based on coexisting infection at sites other than the study injury (with or without antibiotic treatment), potential risk factors for subsequent infection including diabetes, immunosuppression from steroids or other medication, HIV or other infection, or a traumatic brain injury. Patients can have other fractures including those to the spine, upper extremity, contralateral lower extremity, ipsilateral pelvis, hip, femur, or foot. Patients can be treated initially with a temporary external fixator before randomization. They can also be treated initially at an outside institution as long as definitive treatment is provided at the enrolling study center. Patients with bilateral injuries meeting inclusion criteria can be included but only the limb rated as "most severe" by the treating surgeon is enrolled in the study.

Participants meeting eligibility criteria are approached for informed consent in the hospital before definitive fixation. METRC has adopted a comprehensive informed consent process for all of its studies that involves an orthopaedic trauma surgeon, a clinical site research coordinator, and material and resources for patients and family members to facilitate informed decision making about participation (see **Fig. 1**, **Supplemental Digital Content 1**, http://links.lww.com/BOT/A855). In this study, patients and their family members view a brief video that provides a standardized description of the 2 treatments and what study participation involves. If patients refuse randomization, the research team is instructed to wait 24 hours before approaching the patient again for enrollment into the OBS study. This delay in consent for the OBS arm of the study helps ensure that priority is given to the randomized study and discourages sites from preferentially enrolling into the OBS study. A legally authorized representative is permitted to consent on behalf of patients who are unable to do so before definitive fixation.

Sample Size

The sample size for the RCT is based on a 2-group comparison of the probability of rehospitalization for at least 1 of 7 predefined complications (listed below) by 1 year. It was assumed that the probability of rehospitalization in the internal fixation arm would be 60% based on the Lower Extremity Assessment Project data.[1] Using a 2-sided 0.05-level test of the null hypothesis of no treatment difference, it was determined that 140 patients per arm would provide 90% power to detect a 20% absolute reduction (35% relative reduction) in the probability of rehospitalization for the ring fixator arm. With 1 interim analysis using an O'Brien-Fleming boundary, the number of patients was inflated by 1% to preserve the overall type I error. Accounting for 10% missing data, we arrived at our proposed sample size of 156 per arm. To achieve 80% power, the sample size required would be 121 per arm.

For the secondary infection end point, the proposed sample size (assuming 10% missing data, 5% type I error) yields 80% power to detect a difference between infection probabilities at 1 year of 29% versus 14% for the internal and external fixation arms, respectively.[3] This represents a 50% relative reduction in infection rates. With regard to the noninferiority hypotheses (tested at the 5% type I error level), the planned sample size yields a 95% chance of declaring noninferiority if the noninferiority margin is equivalent to an effect size of 0.4 and there is no difference between treatment groups. For the Short Musculoskeletal Function Assessment (SMFA), an effect size of 0.4 is equal to a difference in treatment-specific means of 6 and a common standard deviation of 15. Eighty percent power is achieved at a noninferiority inferiority margin equivalent to an effect size of 0.3.

Protocol Changes

Due to the observation early in the study that many of these severely injured patients were still undergoing treatment of their tibia 12 months after injury, the protocol was modified to extend follow-up for an additional year. Participants with a fracture that heals by 12 months are asked to complete telephone interviews at 18 and 24 months to assess overall function, quality of life, and health services obtained at facilities other than the index hospital. Patients whose fracture has not healed at the time of the 12-month assessment but for whom documentation indicates subsequent healing (based on a clinical and radiograph assessment) are also followed with a telephone interview only. If at the time of the 18- and 24-month follow-ups, there is no documentation of clinical and radiographic healing, participants are asked to return to the clinic for both a clinical examination and interview.

METHODS: TREATMENT ARMS

Both treatments are considered standard of care, and therefore surgical procedures do not require a protocol. In designing the study, it was clear that many surgeons, while familiar with external fixation in general, were less familiar with use of ring fixators for definitive fixation. For this reason, the study mandated that all surgeons applying external ring fixators to study patients must have either completed 5 or more cases before initiation of the study, completed a formal training course in ring fixation, or operate at a site where a surgeon with significant previous experience (>5 cases) has indicated willingness to serve as a mentor. The study team provided training on modern ring external fixation to 39 site investigators before the start of the trial.

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The clinical course of the patients in both arms of the study follows standard protocols for treating skeletal injuries including the provision of antibiotics and use of prophylaxis against thrombo-embolic disease. Minor variability in practices, such as duration of postoperative antibiotics, type of antibiotics, immobilization, and duration until weight bearing is allowed at the discretion of the operating surgeon. Other details regarding the rehabilitation protocol are also left to the discretion of the operating surgeon. This flexibility imparts some variation in care across centers, but realistically mimics the current clinical standard for the best care possible in each of the treatment arms. Block randomization within centers helps to minimize the potential bias introduced by differences in practice by site. Furthermore, relevant details regarding treatment of both the study injury and associated injuries are recorded and will be used in the analysis as necessary to balance comparisons between groups.

Modern Ring External Fixator

For this study "modern ring external fixator" is defined as any fixator that has at least 1 ring proximal and 1 ring distal to the fracture site (Fig. 1). The rings can be connected to the tibia using any combination of external fixation pins or wires at the surgeon's discretion. At least 2 pins or wires must be connected to each ring. Any FDA-approved ring fixator meeting this definition from any manufacturer is allowed. Depending on the preference of the treating surgeon, either distraction osteogenesis or delayed bone grafting can be used to treat large bone gaps. Patients with bone defects treated using distraction osteogenesis use standard techniques, with minor details of the process left to the discretion of the treating surgeon.

Some patients who are randomized to the ring external fixator may be judged by the treating surgeon to not require a flap if the limb were shortened and/or rotated acutely and then lengthened again once the soft tissue has healed. The decision to attempt this technique is left to the treating surgeon, as are all other technical details of the treatment with external fixation. It is anticipated that definitive fixation for some patients in the modern ring fixator group will be delayed (on the order of weeks) while the soft tissue heals in patients with flaps as it is difficult to do dressing and vacuum-assisted closure (VAC) changes around a ring fixator. Common practice is to leave the patient in a temporary external fixator and convert to a modern ring fixator several weeks later once the soft tissue issues have resolved.

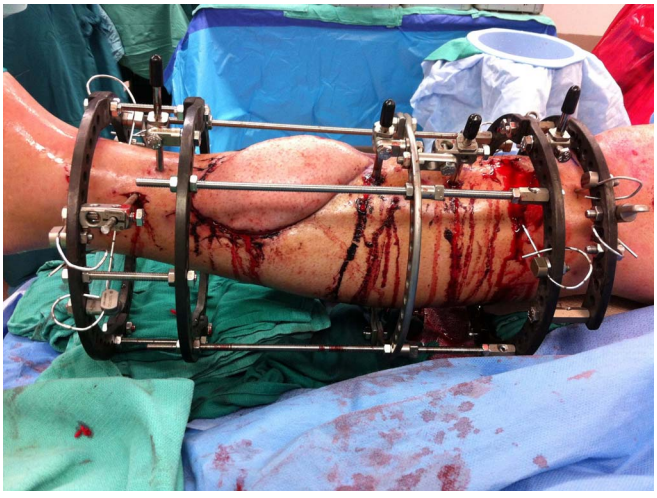

FIGURE 1. Modern external fixation.

Internal Fixation

Definitive treatment is with either a locked IM nail and/or plate at the discretion of the treating surgeon. Although this introduces some heterogeneity into this treatment arm, it is a necessary compromise given the rarity of these injuries coupled with the technical challenge these injuries present. Furthermore, the important commonality of interest in this study is the placement of hardware at the fracture site (introduced by both plates and nails) in contrast to ring fixators that do not involve placement of hardware at the fracture site. Diaphyseal fractures typically receive a locked IM Nail. At least 1 interlocking screw proximal to and 1 interlock distal to the fracture site is required. The nail can be placed with either a reamed or unreamed technique. The FDA-approved nail can be from any manufacturer. Metaphyseal fractures, especially those with fracture lines extending near or into the joint, are often treated with plate fixation. The FDA-approved plate can be from any manufacturer. The plate can be applied in an open or percutaneous fashion, and any combination of locked and/or nonlocked screws can be used. Massive bone defects are treated with delayed bone grafting using existing protocols at the surgeon's discretion.

Crossover is anticipated to be rare but could occur if patients refuse their allocated treatment or if the clinical situation changes after randomization but before definitive fixation. This can occur, for example, if the patient is assigned to internal fixation, but a deep surgical site infection develops at the open fracture site before fixation. In this situation, some surgeons might be uncomfortable placing an IM nail into a recently infected surgical bed and would prefer a change to a ring fixator. Some patients who receive internal fixation as their definitive treatment and then subsequently become infected may have the infection treated with nail removal and use of a ring fixator; these patients will not be considered as crossovers as long as the definitive surgery was consistent with the treatment assignment.

METHODS: DATA COLLECTION AND OUTCOME MEASURES

Baseline Assessment and Frequency of Follow-up Assessments

Data collection at baseline (during the index hospitalization after fracture fixation) are summarized in **Supplemental Digital Content 4** (see **Table 1**, http://links.lww.com/BOT/A858) and include patient characteristics and preinjury health, classification of study and nonstudy injuries, and treatment parameters, including details regarding definitive fixation and postoperative alignment.

Participants return for follow-up study visits at 6 weeks and at 3, 6, and 12 months after injury. Based on the change

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in protocol described above, 18- and 24-month assessments are also obtained either by telephone or in-person clinic visit depending on evidence of fracture healing. In addition to the scheduled study visits, all hospital readmissions and outpatient surgical procedures related to the study fracture are prospectively recorded for 24 months after the injury (through review of the medical record). To estimate the treatment cost, sites are also asked to provide medical bills for the initial hospital stay, readmissions, and outpatient surgeries related to the injured leg.

Primary Outcome

The primary study outcome is defined as having a major complication that results in either: (1) operative treatment during the index hospitalization; (2) rehospitalization during the 12 months after injury (involving operative or nonoperative treatment of the complication); or (3) same day surgery during the 12 months after injury. Major limb complications include 7 predefined occurrences: infection, flap failure, amputation, non-union, malunion, loss of reduction, or hardware failure as diagnosed by the treating surgeon. All complications are reviewed by the centralized adjudication committee to ensure appropriate classification. Complications not classified as major by the definition above are recorded but not included in the definition of the primary outcome. Of note, a superficial infection or pin tract infection is only counted as a major complication if it results in a hospital admission for administration of antibiotics.

Secondary Outcomes

Secondary outcomes are described below; the timing of assessments is summarized in **Supplemental Digital Content 4** (see **Table 1**, http://links.lww.com/BOT/A858).

Infections

Infections are categorized according to standard Centers for Disease Control and Prevention definitions of surgical site infection.[33,34] Deep infections are defined as those that require operative treatment; superficial infections are those treated only with antibiotics and wound care, and no operative treatment for the infection. All cases of infection collect the same information recorded on the METRC infection case report form (CRF) to help adjudication of this outcome.

Fracture Healing

Healing is determined by the treating surgeon based on the modified radiographic union scale in tibias (mRUST) and clinical assessments.[35,36] Due to acknowledged uncertainty of these assessments, surgeons grade the radiographic, clinical, and overall assessment of fracture healing together with their certainty of these assessments.

Limb Function

Assessments of weight-bearing status, ambulation, and range of motion at the knee and ankle are measured by independent research coordinators using goniometers. Self-selected waking speed is also assessed.[37] Participants are timed as they walk 30 feet as quickly as they can with or without the use of an assistive device.

Pain

Pain is measured using the Brief Pain Inventory (BPI), a widely used, 15-item measure of pain intensity and interference with daily life.[38]

Patient-Reported Outcomes

Lower extremity function and health-related quality of life are ascertained using the Short Musculoskeletal Function Assessment (SMFA) and the Veterans RAND 12 Item Health Survey (VR-12).[39,40] To assess higher levels of physical activity, the Paffenbarger Activity Scale (PPAQ) is administered at 12 months.[41] Return to usual major activities is assessed by asking patients what they were doing most of the time during the week before the follow-up visit. The presence of depressive symptoms is evaluated using the 9-item depression scale of the Patient Health Questionnaire (PHQ-9), a well-validated tool for assisting clinicians in diagnosing depression[42] and symptoms of post-traumatic stress disorder (PTSD) are assessed using the standard PTSD Checklist, 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).[43] Satisfaction with treatment is measured using the Short Form Patient Satisfaction Questionnaire (PSQ-18).[44]

Treatment Costs are derived using standard approaches developed for all METRC studies. Case report forms document the initial admission and subsequent readmissions including data on inpatient length of stay, intensive care unit stay, number and type of surgeries, and type of facility (eg, acute care, rehabilitation, skilled nursing). Patient self-reported data on use of outpatient services and paid caregivers is also collected at 3-month intervals. Hospital bills (UB04) are obtained for admissions to METRC facilities. Billed charges are converted to costs based on Medicare cost-to-charge ratios. Costs of inpatient care at METRC facilities will be modeled as a function of patient demographics and characteristics of the hospital episode and used to estimate costs of inpatient care at non-METRC hospitals (for which bills were not obtained). The cost of outpatient care will be estimated by multiplying self-reported use of specific services by per unit costs derived from a national database of paid claims (Truven MarketScan) matched on patient demographics and injury characteristics. Indirect costs attributable to the value of lost productivity and time allocated by informal caregivers will also be estimated using standard human capital approaches.

Monitoring and Quality Assurance

The monitoring plan is designed to verify site compliance with the protocol and with study-specific standard operating procedures (SOPs). The plan facilitates compliance with good clinical practice guidelines (5.18.1). An independent data safety monitoring board reviews study progress, all reported complications, and serious adverse events during meetings held twice a year, or more often as necessary. The chair of the data safety monitoring board serves as the

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Medical Monitor who reviews each serious adverse event as it is reported in real-time (see **Fig. 2**, **Supplemental Digital Content 2**, http://links.lww.com/BOT/A856).

METHODS: DATA MANAGEMENT AND ANALYSIS

Data Management

Data are collected by site research coordinators and clinical investigators using paper case report forms designed specifically for this study and then entered into REDCap (see **Fig. 3**, **Supplemental Digital Content 3**, http://links.lww.com/BOT/A857).

Data Analysis

The main statistical analyses will focus on patients enrolled in the RCT and be conducted according to the intent-to-treat paradigm, which means that all patients will be analyzed according to the treatment group to which they were randomized. The first 2 hypotheses will be evaluated using 2-sample testing procedures at the 5% type-error level; estimates of the treatment effects will be reported along with 95% 2-sided confidence intervals. Rehospitalization for major limb complications will be analyzed as both a binary (any rehospitalization) and a count (number of rehospitalizations) variable. Also used will be statistical procedures that use baseline covariates that are predictive of outcomes (eg, arterial damage, skin damage, contamination, and bone gap) to increase statistical precision (ie, power).[45] Regression modeling may be used if concerns about confounding arise, because of unexpected imbalances between treatment groups with respect to key prognostic baseline factors. Hierarchical modeling will be used if concerns regarding the clustering of outcomes within centers emerge. With regard to the noninferiority hypotheses, 95% one-sided, lower confidence intervals for the treatment differences will be developed and evaluated to assess whether the bound is above the specified noninferiority margin. As secondary analyses, a newly developed procedure may be introduced that uses data from observational patients to construct a more precise estimator of the treatments in the RCT.[45,46] If necessary, secondary analyses will also be conducted to address treatment crossovers.

Multiple imputations will be used to handle missing baseline covariates. Missing outcomes will not be imputed. Sensitivity analyses will be performed to evaluate the robustness of the trial results to various assumptions about the distribution of missing outcomes.[46]

DISCUSSION

The literature does not provide strong conclusions regarding the best treatment for open tibia fractures; evidence to support best treatment practices for the less prevalent and more devastating "severe" open fractures is even less conclusive.[47] A major strength of this study is its broad generalizability as it includes patients treated at multiple level I trauma centers across the United States. Another strength of this study is its randomized design. In an observational study, many centers would be inclined to only use ring fixation to treat the most severely injured thereby biasing results. In addition, at the time this study was initiated, only a few sites had significant experience treating open tibia fractures with a ring fixator. Thus, if patients were not randomized, results would only apply to a few select sites performing the rings and to the unique patient populations they treat. A randomized trial performed at many sites with varying ring fixator experience and different patient populations provides the strongest evidence to inform clinical practice.

Large multicenter randomized treatment trials in the United States are rare in high-energy orthopaedic trauma patients. Many trauma patients are young men, often of low socioeconomic status which presents challenges to enrollment and follow-up. Success in achieving target sample sizes and good follow-up has been demonstrated by the SPRINT, FAITH, and FLOW studies.[48–50] However, the treatments in these previous studies were similar in nature (eg, reamed vs. nonreamed nails in the SPRINT trial) and surgeons are typically equally familiar with performing either one. This was not the case in FIXIT—ie, patients are asked to be randomized to having their fixation inside their skin versus sticking out of their skin for many months. To address the concern that patents would be unwilling to randomize based on strong preferences for one treatment or the other, an observational cohort study is included as was conducted in the SPORT trial which compared operative with nonoperative treatment of spinal conditions. The SPORT studies consented approximately 50% of patients to the randomized study (vs. observational study) but had difficulty with adherence to assigned treatments that we anticipate will be much less of an issue in the FIXIT study.[51]

Since there is also differential experience with modern ring external fixation versus internal fixation among surgeons across treatment centers at the start of the study, there is some concern about the surgeon's willingness to participate and their ability to discuss the study without biasing the patients against randomization. To address this concern, several steps were taken. First, a standardized video that explains the 2 treatments was produced. Research coordinators typically show this video to the patients at the bedside before obtaining consent. Second, educational sessions regarding modern ring fixation techniques were offered by the FIXIT investigators and all surgeons unfamiliar with the techniques were encouraged to attend formal courses. In addition, METRC provided training on active listening to promote best practices for consenting patients. Finally, randomization was performed by site and not by surgeon. Therefore, each site only needs 1 surgeon who is comfortable with ring fixation to perform the surgery for patients randomized to ring fixation.

There are several notable limitations to the study design. First, differential surgeon experience with either treatment may impact the rate of complications or other outcomes. This may bias the results against ring fixation as some surgeons are doing their first fixators as part of this study, whereas all surgeons have extensive experience with plates and nails before the initiation of the study. To examine the potential for this effect in the primary analysis, surgeons

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were surveyed about the number of procedures they conducted before the start of the study. This information will be used in subgroup analyses to explore the impact of experience on results.

In addition, the study was designed using pragmatic principles; details regarding surgical procedures or postoperative care are not protocolized. This approach was used to increase the likelihood of surgeon participation and to allow surgeons to perform what they think is the best possible care for each patient. Indeed there has been broad surgeon support for the study and many centers are able to enroll patients. However, there is some heterogeneity in the details of care which are mitigated to some extent by randomizing within treatment center. This heterogeneity best reflects current practice and will likely increase the adoption of the findings into clinical practice. Finally, the evaluation of 24-month outcomes will be limited to patients who agreed to the extended follow-up after the protocol modification went into effect.

The best treatment for severe open tibia fractures has remained an important debate for decades. This study with its rigorous methodology should provide important and clinically convincing information regarding the treatment of these fractures with modern external ring fixation versus internal fixation. It is also likely that many of the findings from this study can be extrapolated to other less severe injuries, further increasing the impact of this study.

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