pGO-Tibia

A Masked, Randomized Controlled Trial to Evaluate Local Gentamicin versus Saline in Open Tibia Fractures

pGO-Tibia: a masked, randomized controlled trial evaluating Gentamicin versus saline in Open Tibia fractures

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Pilot GO Tibia PROTOCOL

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
CI	Confidence interval
CRF	Case report form
CRP	C-Reactive Protein
DSMC	Data Safety and Monitoring Committee
EQ-5D	EuroQol-5 Dimensions, 3-level questionnaire
FIX-IT	Function Index for Trauma
FRI	Fracture-Related Infection
GO Tibia	Gentamicin versus No antibiotic for the treatment of Open Tibia fractures
GA	Gustilo Anderson
HIC	High-Income Country
IGOT	Institute for Global Orthopaedics and Traumatology
IRB	Institutional Review Board
LMIC	Low- and Middle-Income Country
MOI	Muhimbili Orthopaedic Institute
mRUST	Modified Radiographic Union Score for Tibia
MUHAS	Muhimbili University of Health and Allied Sciences
NIMR	National Institute for Medical Research
PMMA	Polymethylmethacrylate
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SAP	Statistical analysis plan
SSI	Surgical site infection
SC	Steering Committee
UCSF	University of California San Francisco

STUDY SUMMARY

Methodology	Masked, randomized controlled-trial
Coordinating Center	This study will be centrally coordinated by the Institute for Global Orthopaedics and Traumatology, University of California San Francisco (UCSF).
Clinical Site	Muhimbili Orthopaedic Institute (MOI), Dar es Salaam, Tanzania.
Background	The prevention of surgical site infections is important in patients with open fractures, as these wounds are often contaminated. Standard practice in the management of open fractures includes preoperative systemic antibiotics and surgical debridement. In addition to systemic antibiotics, local antibiotics applied directly to the surgical site have shown promise in reducing the rate of fracture-related infection (FRI). Gentamicin is a widely available, low cost antibiotic that holds promise for this application, but high-quality evidence supporting its use is lacking.
Objectives	The overall objective of this research program is to compare the effectiveness of intraoperative, locally administered gentamicin with no antibiotics for the management of open tibia fractures as measured by *occurrence of fracture-related infection (FRI)* (primary outcome) and *occurrence of nonunion and unplanned fracture-related reoperations* (secondary outcomes). The pilot trial specifically aims to assess feasibility of the definitive trial, including enrollment, retention, and data completeness.
Diagnosis and Main Inclusion Criteria	All patients 18 years of age or older who present to Muhimbili Orthopaedic Institute (MOI) for treatment of Gustilo-Anderson (GA) Type I, II or IIIA open tibia fractures will be screened for participation. Eligible patients must present to the hospital within 48 hours of their injury and receive surgical debridement of their open fracture wound within 7 days of their injury. The open wound must be primarily closable at the index debridement.
Treatment Groups	The pGO-Tibia trial will compare two solutions: 1) aqueous gentamicin solution (2mg/mL) in normal saline, or 2) normal saline only. A minimum of 5mL and a maximum of 40 mL of either solution will be injected into the fracture site immediately following primary closure of the traumatic wound.

Randomization	Allocation to the study groups will be performed using a web-based randomization. The randomization sequence was generated using randomly permutated blocks of 4, 6, and 8 with a 1:1 allocation ratio.
Study Outcomes	The definitive trial primary outcome is occurrence of FRI. Secondary outcomes of the definitive trial are the occurrence of 1) nonunion, and 2) unplanned fracture-related reoperation within 12 months of definitive fixation. Definitive trial subsidiary outcomes include health-related quality of life, radiographic healing, and clinical healing. A blinded adjudication process will judge each study event on occurrence of FRIs, nonunions, and unplanned fracture-related reoperations.
Feasibility Outcomes	This pilot trial will focus on the following feasibility endpoints: Recruitment: number of patients screened, number and proportion of patients screened that are eligible, enrolled, randomized, and receive intervention. Retention: number and proportion of randomized patients who attend each follow-up visit. Data collection completeness, solution quality control, masking and concealment, and evaluation of primary and secondary outcomes (reliability of fracture-related infection and mRUST scoring, radiographic image quality, and completeness of EQ-5D and FIX-IT).
Follow-Up	Study participants will be followed at 2 weeks, 6 weeks, 3 months, 6 months, 9 months, and 12 months from their fracture.
Sample Size	50 individuals per arm will be included in the feasibility trial.
Significance	FRIs place a significant burden on both the patient and the healthcare system, as they increase patient mortality, delay healing, decrease functional outcomes and health-related quality of life, and often require prolonged hospitalization or reoperation, increasing the cost of care. Given the consequences of open fracture complications, maximizing the effectiveness of prophylactic procedures is essential. The GO Tibia trial will provide necessary evidence to guide the use of local antibiotic application in prevention of FRIs in open fractures,

	and may significantly impact care and outcomes of open extremity fractures.

1.0 INTRODUCTION

1.1 Open Tibia Fractures

Open tibia fractures often result from high-energy trauma[1]. These fractures represent an orthopaedic emergency associated with high morbidity and mortality. Fracture management includes systemic antibiotic prophylaxis, tetanus booster, wound irrigation and surgical debridement, and fracture stabilization[2,3]. Open fractures are contaminated[1], and even with prompt treatment, infection can occur in up to 40% of cases[3,4,5]. SSIs place a significant burden on both the patient and the healthcare system, as they increase patient mortality, delay healing, decrease functional outcomes and health-related quality of life, and often require prolonged hospitalization or reoperation, increasing the cost of care[6,4,7].

1.2 Prevention of Infection

Because surgical site infections have such profound consequences, prevention is crucial. Intravenous antibiotics are essential in reducing the risk of infection, but their dosage is limited by systemic toxicity, and local concentrations are diminished by the compromised blood supply at the site of injury[5]. Local antibiotics administered intraoperatively directly in the traumatic wound offer an additional method of infection prevention[8–10]. A recent meta-analysis found decreased incidence of infection in both spine and trauma surgeries, but this effect was absent with more rigorous study designs[11]. This study demonstrated that vancomycin significantly reduces gram-positive infections without appearing to affect the incidence of gram-negative infections, which are the second most common pathogen in SSIs after open fracture[11]. In addition, the relatively high cost of vancomycin may prohibit widespread use, particularly in low-income countries.

1.3 Rationale for Intrawound Antibiotics and Gentamicin Use

Some promising alternatives to vancomycin are aminoglycoside antibiotics, including gentamicin. These antibiotics are on the order of 10-100 times cheaper than vancomycin, with pricing in Tanzania less than $0.50 for one 80mg vial of liquid gentamicin compared with approximately 20 USD for 1g of vancomycin powder[12]. Aminoglycosides cover a broad spectrum of gram-negative and gram-positive bacteria, including both staphylococcus aureus and coagulase-negative staphylococcus, the two most common bacteria in fracture-related infection (FRI)[13]. Aminoglycosides impregnated into polymethylmethacrylate (PMMA) beads have been shown to reduce infection in open fractures, but a second surgery is required to remove the beads[14]. PMMA also costs $80-100 per 40-gram bag, which can be cost-prohibitive in low-resource settings.

A lower-cost alternative is injection of aqueous aminoglycosides after wound closure. Reduced rates of infection have been observed after local gentamicin injection in an animal model[15] and

one large retrospective cohort study found a 50% reduction in the odds of deep and superficial infection after prophylactic local injection of aminoglycosides for open tibia fractures compared to no local antibiotics[16]. Although promising, the latter study's limitations are numerous, including retrospective, non-randomized design, absence of masking, and variability in treatment protocols and definitions of infection. There remains a clear gap in knowledge regarding the efficacy of locally-administered gentamicin in preventing fracture-related infection in open fractures.

The *GO-Tibia trial, A Masked, Randomized Controlled Trial to Evaluate Local Gentamicin versus Saline in Open Tibia Fractures*, will address these gaps in the literature.

2.0 STUDY AIMS AND HYPOTHESES

The study described herein is a single-center pilot trial to evaluate the feasibility of necessary protocols including, recruitment, retention, masking and concealment, intervention, and follow-up. The described pilot study will establish effect sizes for appropriate power calculations for a subsequent definitive trial.

The overarching objective of the definitive trial is to test whether injection of intraoperative local gentamicin impacts the rate of fracture-related infection following GA Type I, II or IIIA open tibia fractures in Tanzania. We hypothesize that the risk of fracture-related infection will be reduced by the intraoperative use of locally administered gentamicin at the time of wound closure.

2.1 Definitive Trial Specific Aims:

1. Compare the rate of fracture-related infection at one year after intraoperative local gentamicin injection or intraoperative local saline injection among adults treated operatively for GA Type I, II, or IIIA open tibia fractures. [Primary aim]

2. Compare the occurrence of 1) nonunion, and 2) unplanned fracture-related reoperation after intraoperative local gentamicin injection or intraoperative local saline injection among adults treated operatively for GA Type I, II, or IIIA open tibia fractures. [Secondary aims]

3. Evaluate the economic impact of fracture-related infection (FRI) after open tibia fractures in Sub-Saharan Africa including direct medical costs and lost productivity. [Secondary aims]

Null hypothesis: There is no difference in the rate of fracture-related infection between local gentamicin administration and saline administration for adult patients with GA Type I, II, or IIIA open tibia fractures treated in Sub-Saharan Africa.

Alternative hypothesis: Intraoperative local gentamicin administration decreases the occurrence of fracture-related infection in adult patients with GA Type I, II, or IIIA open tibia fractures treated in Sub-Saharan Africa.

2.2 Feasibility Trial Specific Aims:

Outcomes include rates of screening, enrollment, randomization, allocation, reliability of intervention, subject retention, and data completeness.

Specifically, feasibility outcomes are:

1. Recruitment: number of patients screened, number and proportion of patients screened that are eligible, enrolled, randomized, and receive intervention.

2. Retention: number and proportion of randomized patients who attend each follow-up visit. We aim for an adherence rate at follow-up of 80% at one year.

3. Data collection completeness: proportion of fracture-related infection criteria, EuroQol-5 Dimensions, 3-level questionnaire (EQ-5D), Function Index for Trauma (FIX-IT), and Modified Radiographic Union Score for Tibia (mRUST)[17] indices complete at each time point.

4. Solution quality control: confirmation of the ongoing sensitivity of standard organisms to trial solutions via interval testing.

5. Masking and concealment: determination of the continued masking of surgeons to solution identity via intraoperative surgeon survey.

6. Evaluation of primary and secondary outcomes: reliability of fracture-related infection and mRUST scoring[17], radiographic image quality, and completeness of EQ-5D and FIX-IT.

3.0 TRIAL DESIGN

3.1 Summary:

In the accompanying Clinical Research Protocol and Standard Operating Procedures document, we describe the protocols and procedures for a feasibility pilot trial for implementing a single-center, double-masked, individually randomized, placebo-controlled study on the efficacy of intraoperative local gentamicin for the prevention of fracture-related infection in open Gustilo-Anderson Type I-IIIA tibial fractures. The Clinical Research Protocol and Standard Operating Procedures document includes general trial information, aims and objectives, study design, trial procedures (including recruitment, enrollment, consent, randomization, masking, intervention, and follow-up protocols), and data management.

4.0 METHODS

4.1 Study Setting:
The GO Tibia randomized controlled trial will be conducted at the Muhimbili Orthopaedic Institute (MOI) in Dar es Salaam, Tanzania. MOI is a tertiary referral hospital with large catchment area and high volume of adult musculoskeletal trauma that, combined with its strong leadership and prior trial experience, has the capacity to manage this large-scale RCT.

4.2 Eligibility Criteria:
All patients presenting to the MOI emergency department age 18 years and older with an open tibia fracture will be screened for eligibility (Table 1). After surgical debridement, the surgeon will assess the wound to see if the wound can be primarily closed. If the wound can be primarily closed, the patient will continue with the RCT Study. If the wound cannot be primarily closed, the patient will be excluded from the study.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Skeletally mature patients (>18 years old)	1. Time from injury to presentation > 48 hours
2. Open tibial shaft fracture meeting the following criteria:	2. Time from injury to surgery > 7 days
a. OTA Type 42	3. Aminoglycoside allergy
b. Primarily closable wound	4. GA IIIB or IIIC open fractures
c. GA I, II, or IIIA	5. Bilateral open tibial fractures
	6. Severe brain (GCS<12) or spinal cord injury
	7. Severe vascular injury
	8. Severe burns (>10% TBSA or >5% TBSA with full thickness or circumferential injury)
	9. Pathologic fracture
	10. History of active limb infection, ipsilaterally
	11. Unlikely to complete follow-up

Abbreviations: Orthopaedic Trauma Association (OTA); Gustilo-Anderson (GA); Glasgow Coma Scale (GCS); Total body surface area (TBSA)

4.3 Recruitment Strategy and Patient Screening:
Recruiting patients: All adult (over age 18) patients admitted to MOI for acute open tibia fracture will be considered for inclusion in this study. Patients will be evaluated by the on-call orthopaedic surgery resident. The study protocol will be introduced to the patient either by the

resident or research coordinator. Patients interested in enrolling will be consented. All consenting patients will be treated per institutional protocol with immediate systemic ceftriaxone administration for open fracture prophylaxis and urgent debridement and bony stabilization with either internal or external fixation at the discretion of the operating surgeon. The study protocol will not influence the surgical plan for management of study participants. Type of fixation will not affect participant inclusion or study protocol.

The surgeon will make a final assessment of the wound and exclude patients with a wound that is not amenable to primary closure. If the wound is determined amenable to primary closure, participants will be randomized intraoperatively by research coordinators after closure is complete to receive intra-operative local injection of either aqueous gentamicin solution (intervention) or normal saline solution (control).

4.3.1 Patient Retention

Study participants will not be directly financially compensated and will incur the standard fees for evaluation and treatment. To decrease the financial burden and increase follow-up, however, the following as described will be provided for study participants:

- Systemic antibiotics (Ceftriaxone) cost during first hospital stay will be covered for all patients screened for the study
- Gentamicin (intervention arm only), saline solution, and injection materials (syringes, needles) will be covered for all participants
- Preoperative, postoperative, and 2-week creatinine levels will be covered for all participants
- C-reactive protein (CRP) levels will be covered for all participants
- Radiograph cost: Radiographs of the affected extremity will be obtained at the time of presentation and at post-operative follow-up appointments to adequately monitor healing. Imaging costs will be covered for all study participants.
- Post-operative consultation fees: consultation fees for study participant follow-up clinical evaluations will be waived for study participants.
- Follow-up visits will take place in a dedicated study clinic to minimize wait times
- Three separate contacts will be obtained for each patient upon enrollment.
- Follow-up clinic visit reminders will be given via phone call and by text message during the week prior to each visit
- Reoperation fees: The cost of two intraoperative cultures will be covered for study participants who undergo reoperation.

4.4 Schedule of Events:

Following participant enrollment and informed consent, baseline clinical and demographic data are collected from the patient including socioeconomic status, medical and social history, injury characteristics, and estimated pre-injury health-related quality of life. Contact information for the patient and at least two close contacts is collected to optimize follow-up. Pre- and post-operative

radiographs will be obtained prior to hospital discharge and serum creatinine will be obtained pre-operatively and on postoperative day 2. If serum creatinine levels on postoperative day 2 are ≥1.5 times patient baseline and acute kidney injury is suspected, serum creatinine levels will be redrawn at two-week follow-up visit[18]. Personnel time and resources utilized will be directly observed using time and motion analysis, beginning from patient admission to the completion of surgery and transfer to the ward. The schedule of patient encounters and corresponding data to be collected is described in Table 2.

Participants will return to clinic for follow-up at 2 weeks, 6 weeks, 3 months, 6 months, 9 months, and 1 year following surgery.

Specifically, follow-up visits will include the following:

1. Two-week postoperative visit: The study investigator will review and record interval history since hospital discharge. The patient will complete a Visual Analog Scale for pain assessment. A physical examination will be performed to assess for signs of Fracture-related Infection. C-reactive protein level will be obtained. If serum creatinine levels on postoperative day 2 are ≥1.5 times patient baseline and acute kidney injury is suspected, serum creatinine levels will be redrawn.
2. Six-week postoperative visit: During the follow-up visit reminder telephone phone call, the study investigator will ask the five fracture-related infection (FRI) validation questions. At the visit, the study investigator will review and record interval history since the last appointment. The patient will complete a Visual Analog Scale for pain assessment. The study subject will complete a Work Productivity and Activity Impairment questionnaire (WPAI) to assess lost productivity, and patient reported outcome measure (EQ-5D). A physical examination will be performed to assess for signs of fracture-related infection (FRI). C-reactive protein level will be obtained.
3. Three-month, six-month, nine-month, and 12-month postoperative visits: During the follow-up visit reminder telephone phone call, the study investigator will ask the five five fracture-related infection (FRI) validation questions. At the visit, the study investigator will review and record interval history since the last appointment. The patient will complete a Visual Analog Scale for pain assessment. The study subject will complete a Work and Activity Impairment questionnaire (WPAI), the FIX-IT score for clinical healing, additional questions to address indirect costs and economic impact associated with their treatment, and patient reported outcome measure (EQ-5D). A physical examination will be performed to assess for signs of fracture-related infection (FRI). AP and lateral radiographs will be taken. C-reactive protein level will be obtained.

Table 2: Schedule of Events

	Hospital				Outpatient					
	Pre-Surgery		Surgery	Post-Surgery						
Assessment	Screening	Enrollment		<= 48hrs Post Op	2-weeks	6-weeks	3-months	6-months	9-months	12-months

Radiographs	●				●			●	●	●	●
Informed Consent		●									
Serum Creatinine*		●			●	●					
Randomization			●								
Intervention			●								
Baseline Data**					●						
Contact Information					●						
EQ-5D					●			●	●	●	●
Outcomes Assessment***						●	●	●	●	●	●
FIX-IT								●	●	●	●
WPAI							●	●	●	●	●
C-reactive protein						●	●	●	●	●	●
Adverse Event Screen						●	●	●	●	●	●

*** 2-week creatinine level will only be drawn if postoperative creatinine level is ≥1.5 times patient baseline and acute kidney injury is suspected

** demographic, medical history, injury characteristics

*** fracture-related infection, unplanned fracture-related reoperation

4.5 Randomization Methods

Allocation to the study groups will be randomly assigned using a web-based randomization tool as part of Research Electronic Data Capture (REDCap). The randomization sequence was generated using randomly permutated blocks of 4, 6, and 8 with a 1:1 allocation ratio.

4.6 Masking:

Trial participants are masked to treatment group allocation. All health care providers involved in care of the trial participants including physicians, surgeons, and nurses are masked to treatment group allocation. Research team members including research coordinators, data collectors, and data analysts, are masked to treatment group allocation.

Masking is established and maintained by preparation of the study solutions in visually indistinguishable syringes labeled either “Solution A” or “Solution B”.

Two UCSF research personnel are unmasked for the implementation and management of trial protocols, but do not have any contact with study participants and are not aware of the treatment group to which each participant is assigned. The study nurse responsible for preparation of study solutions at MOI is also unmasked, but does not have any contact with study participants and is not aware of the treatment group to which each participant is assigned.

4.7 Description of Interventions

4.7.1 Study Solution Preparation and Storage

A certified study nurse, who is one of three un-masked personnel, will prepare aqueous gentamicin and normal saline solutions. The gentamicin solution consists of 2mg/mL aqueous gentamicin while the control solution consists of normal saline without active agent.

The working solutions are prepared in a locked room using sterile technique and are prepared in identical syringes labeled either "Solution A" or "Solution B", according to the masking key. The masking key is kept in a locked cabinet in a locked office, only accessible by the study nurse. Solutions are labeled with date of preparation and date of expiration. The study nurse maintains a preparation log to ensure the integrity of the study solutions.

Study solutions are stored at 4 degrees Celsius for up to 48 hours, in accordance with pharmacist guidelines. Solutions are stored in a locked, dedicated study refrigerator adjacent to the operating suite. Upon expiration, unused study solutions are discarded and new solutions prepared. The study refrigerator is checked daily by the study nurse and a use log is maintained to ensure the integrity of the study solutions. All gentamicin is obtained from Sichuan Long March Pharmaceutical Co., Ltd (Leshan, Sichuan Province, China) and normal saline is obtained from Otsuka Pharmaceutical India Private Limited (Ahmedabad, India).

4.7.2 Study Solution Administration

Following intraoperative randomization, the appropriate study solution is provided to the administering surgeon in a masked manner. The local solution injection is administered immediately following wound closure. As described previously by Lawing et al[19], the solution is injected by inserting a 22-gauge needle down to bone through an anteromedial approach at the level of the fracture site such that the injected solution fills the wound cavity. A minimum of 5mL of study solution may be injected, and the injection is continued until either extravasation is seen through the traumatic wound or a maximum of 40mL has been administered, whichever occurs first.

For quality control, the efficacy of masked study solutions will be tested against standard organisms. This will occur once per month for the first 6 months and once every 3 months thereafter by the Muhimbili University of Health and Allied Sciences (MUHAS) microbiology lab, with results evaluated by unmasked study personnel.

4.7.3 Perioperative Co-Interventions

Systemic antibiotic prophylaxis

All patients will receive prophylactic systemic antibiotics as soon as possible after presentation to the hospital regardless of whether they participate in the study. Patients will be given a single dose of ceftriaxone 1 gram intravenously, which provides 24 hours of coverage.

Debridement

All patients will undergo systematic debridement of the traumatic wound with removal of devitalized bone and soft-tissue. Wounds will be extended as necessary to remove contaminants and deliver the bone ends from the wound. The wound will be irrigated with a minimum of 2 liters normal saline solution using low-pressure lavage. For cases of severe contamination, the wound may be washed with tap water prior to surgical prep.

Fracture stabilization
Treatment of the fracture will be at surgeon discretion and may be temporizing or definitive using either external fixation (EF) or intramedullary nailing (IMN).

External fixator: A uniplanar external fixator (AO Dispofix) will be used in all cases consisting of a minimum of two Schanz pins proximal to the fracture and two distal pins connected by a single stainless steel bar. The choice to add additional pins or span adjacent joints will be at the discretion of the treating surgeon. At hospital discharge, the patient will be instructed on proper pin-care procedures. The pin care protocol will consist of cleaning each pin using methylated spirits (methyl alcohol) twice daily until the external fixator is removed. The external fixator will remain in place for a minimum of 4-6 weeks and maximum of 3 months.

Intramedullary Nail: The SIGN Standard nail (SIGN Fracture Care International, Richland, WA) will be used in all cases. The nail will be inserted using an infrapatellar approach. Two proximal and two distal interlocking screws will be placed using an external jig. Intraoperative fluoroscopy will not be used.

Wound closure
The wound will be closed primarily when it is felt to be safe and feasible by the treating surgeon. A layered closure will be performed whenever possible using nylon for skin and a braided absorbable suture for the deeper layers.

Postoperative Wound Care

If the wound is dry at the 2-week wound check, the dressing will be removed. If the wound is still wet at 2 weeks, the dressing will be changed and the patient will be instructed to periodically revisit the hospital to change the dressing until the wound becomes dry.

Weight Bearing Protocol

All patients will be advised to be on toe-touch status for the first 6 weeks. Afterwards, the patient will be instructed to bear weight as permitted by pain.

4.6 Description of Data Collection

4.6.1 Data collection
Three trained research coordinators with research and data collection experience will be responsible for all data collection. All data will be uploaded into REDCap (see section **6.0 DATA MANAGEMENT**) using portable laptops and tablet computers.

4.6.2 Overview of Data Collection Instruments

Data will be collected in the schedule described in section 4.4 Schedule of Events, and includes:

- Baseline patient data includes demographic information, such as age, gender, medical history, and injury characteristics.
- The EuroQol-5 Dimensions, 3-level questionnaire (EQ-5D)[20], Swahili version, which is a validated instrument for measuring patient quality of life.
- The Function Index for Trauma (FIX-IT)[21], a validated instrument for evaluating healing in lower-extremity fractures. The scoring system includes a single-leg stand, ambulation, and palpation test.
- The Modified Radiographic Union Score for Tibia (mRUST)[22] is a validated, radiographic measure of bony union.

4.6.3 Wound Measurement and Classification

Wound Measurement and Classification

A measurement of the wound is to be done in the operating room, both before and after debridement. The first measurement will be taken prior to debridement. The second measurement will be taken following surgical fixation but before wound closure. The wound should be measured using a centimeter ruler or the handle of a scalpel (rather than visually approximated).

Only the maximum dimension of the wound (the longest length possible) needs to be recorded. This is irrespective of how the wound is oriented along the limb. The wound length should only include the part of the wound that is open (ignore any superficial abrasions that may be connected to the open part of the wound). In the event that there are multiple wounds, measure each wound that communicates with the fracture and sum the lengths of the individual wounds. *Do not* include the wounds that were made for the purpose of inserting an intramedullary nail or interlocking screws.

OTA and Gustilo-Anderson Wound Classification

Classification of the wound is done using the OTA Wound Classification questionnaire and the Gustilo-Anderson classification of injury severity. Wound classification is to be done after surgical debridement, which allows the surgeon to fully assess the wound.

4.6.4 Radiographs

Orthogonal images will be obtained and digitally copied using screen capture. Images will then be uploaded into REDCap. Radiographs are then sent for review by the adjudication committee, and are assessed for radiographic signs of healing using the mRUST score by two fellowship-trained orthopaedic trauma surgeons. In cases of disagreement between reviewers, decisions are made by consensus.

4.6.5 Economic Analysis

Indirect Cost Assessment
Lost productivity will be assessed using the Work Productivity and Activity Impairment (WPAI) survey modified for lower extremity injury. Employment type, hours worked, and wages earned will be assessed at each time point. Transportation costs associated with the injury and follow up care will be assessed at each time point.

Direct Cost Assessment
Direct costs will be measured using micro-costing methods. Resource utilization and time data will be collected through direct observation using time and motion (TM) analysis and patient charts. Specifically, each of the captured surgical interventions (each treatment strategy as well as reoperation for complication) is divided into discrete steps. For each step, resources used, personnel involved and duration of activity will be directly observed and recorded. This information will be used to assess personnel costs of each surgical procedure. Implant costs will be obtained from the suppliers. Surgical instrument costs will be obtained from the manufacturers, accounting for depreciation by assuming that the lifetime of surgical instruments is 10 years. The cost of intraoperative supplies, such as medications, disposables, intravenous fluids, blood products, and others, will be obtained from the suppliers.

Cost per day of hospital stay will be estimated for three categories: index hospitalization, infected complication hospitalization, and uninfected complication hospitalization. This is based on the assumption that the cost per day of hospital stay will differ between these groups but not significantly within these groups.

Utilization of medications and laboratory and radiology investigations will be assessed from the patient chart. Type and quantity of medications will be obtained from the patient chart, and costs will be obtained from the supplier. Labor and resource costs of laboratory and radiology interventions will be obtained from the hospital laboratory and radiology departments.

4.7 Outcome Measures

4.7.1 Feasibility Trial Outcomes

7. Recruitment: number of patients screened, number and proportion of patients screened that are eligible, enrolled, randomized, and receive intervention.
8. Retention: number and proportion of randomized patients who attend each follow-up visit. We aim for an adherence rate at follow-up of 80% at one year, which was achieved in our previous open tibia fracture trial performed through the same collaborative partnership.
9. Data collection completeness: proportion of fracture-related infection criteria, EuroQol-5 Dimensions, 3-level questionnaire (EQ-5D), Function Index for Trauma (FIX-IT), and

Modified Radiographic Union Score for Tibia (mRUST)[17] indices complete at each time-point.

10. Solution quality control: confirmation of the ongoing sensitivity of standard organisms to trial solutions via interval testing. This will occur once per month for the first 6 months and once every 6 months thereafter by the Muhimbili University of Health and Allied Sciences (MUHAS) microbiology lab, with results evaluated by unmasked study personnel.

11. Masking and concealment: determination of the continued masking of surgeons to solution identity via intraoperative surgeon survey.

12. Evaluation of primary and secondary outcomes: reliability of fracture-related infection and mRUST scoring, validation of telephone criteria for fracture-related infection, radiographic image quality, and completeness of EQ-5D and FIX-IT.

4.7.2 Definitive Trial Outcomes

Primary Outcome

The primary outcome is occurrence of *fracture-related infection* (FRI) a binary variable. FRI diagnosis is likely to peak between 3 and 6 months after surgery and has a non-normal time-to-event distribution, with incident cases rarely presenting later than 12 months after surgery. Any of the four following diagnostic criteria are confirmatory for infection: (1) fistula, sinus or wound breakdown; (2) purulent drainage from the wound or presence of pus during surgery; (3) phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant specimens; or (4) presence of microorganisms in deep tissue taken during an operative intervention, as seen on histopathological examination.

Secondary Outcomes

The following secondary outcomes will be assessed:

1. Occurrence of nonunion, a binary variable, as defined by:
    a. Any unplanned reoperation for promotion of bone healing; OR
    b. mRUST ≤10 AND either: FIX-IT score ≤11 at 12 month follow-up, OR recommendation by treating surgeon for nonunion repair surgery.
2. Occurrence of unplanned fracture-related reoperation, a binary variable, for infection, wound healing, or fracture union, excluding removal of implants for prominence/irritation. This may include but is not limited to:
    a. Irrigation and debridement of surgical incisions or open fracture wounds due to infections or wound healing problems;
    b. Revision wound closure for dehiscence;
    c. Soft tissue coverage procedure for infected or necrotic wound;
    d. Fracture delayed union or nonunion surgery (such as bone grafting or implant exchange);

e. Reoperation for hardware or prosthesis failure due to infection or bone-healing problems;
f. Amputation for infection, wound or fracture healing problem.

Subsidiary Outcomes
The following subsidiary outcomes will be assessed:

1. Radiographic healing via the mRUST score, an ordinal scale ranging from 4 to 16.
2. Clinical healing via the FIX-IT score, an ordinal scale from 0-12 that encompasses two domains, ability to weight-bear and pain at fracture site, each scored from 0-6: ability to weight-bear and pain at fracture site.
3. Health-related quality of life via EQ-5D.
4. FRI suggestive criteria, including clinical (wound redness, fever) and radiographic signs (sequestrum), elevated serum inflammatory markers, and new onset or increased wound drainage.
5. C-reactive protein level, including preoperative level and postoperative level collected over longitudinal time points
6. Direct and indirect costs as measured by Time and Motion analysis and WPAI

Subgroup Analyses
In order to examine the differential treatment effects of local gentamicin administration among clinically relevant subgroups defined by: i) GA classification, ii) severity of wound contamination, iii) time from injury to surgery, and iv) type of definitive fixation, the following subgroup analyses will be performed:

1. Gustilo-Anderson classification of fracture (type 1 or 2 vs 3)
2. Contamination (minimal or moderate versus severe based on the Orthopaedic Trauma Association Open Fracture Classification)
3. Time to surgery (≤24 versus >24 hours after injury)
4. Type of fixation (external fixation versus intramedullary nailing).

4.7.3 Steering Committee and Adjudication

The Steering Committee (SC) for the study will consist of Dr. David Shearer, Dr. Saam Morshed, Dr. Billy Haonga, Dr. Edmund Eliezer, and Dr. Travis Porco (principal trial statistician). The Steering committee will be responsible for performing adjudication review and approving any sub-projects, as outlined below.

Review of the following study events will require review from the members of the study steering committee:

1. Death of a patient
2. Surgical complications requiring reoperation

The review, comment, and voting process will occur on REDCAP. Three steering members will need to evaluate each event that is put up for review. The steering committee members are responsible for providing the following inputs for each event:

1. Comments/opinions/justifications
2. Vote (yes or no): question varies depending on the event
    a. Death event: question not applicable
    b. Surgical complications requiring reoperation: does the patient need a reoperation?
3. Vote (yes or no): is this event a primary outcome of the study?

Adjudication review will be conducted every 2 months.

Additionally, the steering committee will meet monthly to review standardized REDCap data quality reports.

5.0 STATISTICAL PLAN

5.1 Preliminary Sample size determination:

This study seeks to explore if local antibiotics are effective in reducing infection. Existing literature estimates the rate of infection after intramedullary nailing for open-tibia fracture at 6-21%, with higher rates seen in developing countries[23,24]. Based on the previous randomized controlled trial conducted at MOI, the rate of deep infection in patients with open tibia fractures who do not receive local antibiotics during operative management was estimated to be 12%. For a relative risk reduction of 50% in the rate of deep surgical site infections, with an alpha (two-sided) of 0.05 and power of 0.80, the estimated sample size was 712 patients (356 per group). Assuming a loss to follow-up of 20%, the final sample size needed was determined to be 890 patients. Given the anticipated enrollment of 15 participants per month, enrollment would take approximately 5 years for a single center study. The study described herein is a pilot trial with a 1-year enrollment period to include 100 patients, approximately 10-20% of the necessary sample size for the definitive trial.

5.2 Statistical Methods

Feasibility outcomes described in 4.7.1 will be summarized using means and proportions, without the use of inferential statistics. Given the principle feasibility aim of this pilot trial, the following statistical methods are described primarily for planning purposes. Statistical methodology to be performed in the analysis of each primary, secondary, and subsidiary outcome is outlined below. The statistical analysis plan (SAP) will provide additional detail on statistical analysis and will be modified as necessary based on data collected in this pilot trial.

Outcomes Analysis Planned for Definitive Trial

Outcome	Data	Method of analysis

Primary		
Rate of fracture-related infection	FRI criteria	Relative Hazard as estimated by two-sided binomial regression with the complementary log-log link, with a type I error rate (alpha) of 0.05.
Secondary		
Rate of unplanned reoperation	Review of complications	Fisher's exact test on the 2 × 2 cross-tabulation
Rate of nonunion	Nonunion criteria	
Subsidiary		
Quality of Life	EQ-5D	Comparison means of gentamicin-treated group and placebo group using two-tailed students t-test (alpha=0.05)
Inflammatory Markers	CRP	
Radiographic Healing	mRUST	
Clinical Healing	FIX-IT	
Direct costs	TM Analysis	
Indirect costs	WPAI	
FRI Suggestive Criteria	FRI criteria	Fisher's exact test on the 2 × 2 cross-tabulation

5.2.1 Primary pre-specified analysis

Outcome Variable: the occurrence of FRI, as a binary outcome. We will denote this by Y_i, for person i. For each individual, we also record the time under observation, T_i. This value will be censored at the end of the follow-up time.

Primary Analysis: the primary analysis will be conducted as a binomial regression with the complementary log-log link. This allows the available person-time to be used.

The estimated effect will be the relative hazard.

The analysis will be two-sided, with a type I error rate (alpha) of 0.05. Because there is no intention of including patients from this pilot trial into a subsequent definitive study, each trial (pilot and definitive) is completely separate, with an independent alpha.

5.2.2 Additional analyses

Supplemental analyses. These analyses are designed to provide additional insight and support for the primary analysis, and to assess whether or not the methodological choices we made had an undue effect on the results. In reporting, they will be sharply distinguished from the primary outcome, and will not be highlighted as central or determinative findings in reports, publications,

abstracts, posters or other communications.

Additional sensitivity analyses will be conducted based on the following variables as base- line covariates: Gustilo fracture type, lower extremity fracture, wound contamination, time from injury to first debridement, antiseptic wound dressing in the emergency department, method of fixation, wound closure at initial debridement, age, work-related injury, and employment status. Such analyses will be reported descriptively and with confidence intervals, but no significance P-values will be given. Conclusions based on such subgroups or adjustments will be considered hypothesis-generating, and will not form the basis for highlighting in reports or publications.

Fisher's Exact Test. We will report the results of Fisher's exact test on the 2 × 2 cross-tabulation of the reoperation binary outcome and the treatment assignment. This does not take into account observation time. This is an independent statistical procedure, and may yield statistically inconsistent results.°

Risk difference. We will report the 95% confidence interval for the risk difference between the groups. Because this will be conducted by an independent regression (binomial regression with the identity link), these new findings may be statistically inconsistent with the main analysis. Thus, we will only report 95% confidence intervals, omitting P-values. The risk difference is interpretively important and may be useful in future meta-analytic studies.

Combined analysis. At the conclusion of both trials, an additional analysis will be con- ducted in which both data sets are combined into a single analysis. This analysis, bearing similarity to a meta-analysis of original data, will yield a combined effect estimate and confidence interval. deviation. No P-value will be reported. Thus, this secondary analysis does not constitute an additional risk for declaring significance and no multiple comparison adjustment is mandated.

Statistical considerations. Intent to treat analysis is recommended, but impossible when the primary outcome is missing. We will conduct exploratory regression of missingness, and observation time, using the following predictors: gender, severity of injury, distance to clinic, and age.

Secondary analyses. All secondary analyses will be sharply distinguished from the primary pre-specified analysis and will be identified as such. Secondary analyses include outcome variables or planned subsets, which contribute either additional insight or address different scientific questions than the primary analysis.

6.0 DATA MANAGEMENT

6.1 Case Report Forms and Data Transmission

Clinical sites will be provided with the trial case report forms (CRFs) prior to initiation of enrollment. Research personnel at each clinical site will submit the required data, as detailed on

the CRFs, using the Research Electronic Data Capture (REDCap) electronic data capture system. Clinical site personnel will receive a unique login and password.

6.2 Data Integrity

The REDCap system uses a variety of mechanisms for checking data at the time of entry including skip logic, range checks, and data type checks. Interim analyses will serve as a quality control method to assess missing, implausible, or inconsistent data.

7.0 ETHICS AND DISSEMINATION

7.1 Research Ethics Approval

Ethical approval for this trial was obtained from the National Institute of Medical Research, Tanzania (Ref#: NIMR/HQ/R.8a/Vol. IX/2958), and the UCSF Human Subjects Research Internal Review Board (IRB# 17-23950, Ref#: 260102).

The GO Tibia trial was registered at ClinicalTrials.gov (NCT03559400) on June 18, 2018 (https://clinicaltrials.gov/ct2/show/NCT03559400).

Any proposed protocol modifications will be submitted for approval to both ethical review boards.

7.2 Consent

If a patient is deemed eligible for the study, designated study personnel will obtain informed consent from the patient (preferred) or proxy as soon as feasibly possible. The consent process will typically take place in the emergency room, prior to surgical fixation of their open fracture. To discuss their participation, a member of the study team will approach potentially eligible patients.

To obtain informed consent, study personnel should follow the below procedures:

- Present study information in a manner that is understandable to the potential participant.
- Discuss the study with the potential participant and answer any questions he or she asks.
- Allow the potential participant an opportunity to discuss participation with their family, friends, or family physician, if desired.
- Confirm that the participant understands the risks and benefits of participating in the study and that their participation is voluntary.
- Complete and obtain signatures for informed consent form and obtain contact information from the participant.

The process of obtaining and documenting informed consent forms will be completed in accordance with local Good Clinical Practice recommendations.

Upon providing informed consent, study participants will be followed for 12 months from their fracture. Given the short follow-up time, the need for a regular reassessment of consent will not apply; however, participants may withdraw their consent at any time.

7.3 Confidentiality

Information about study participants will be kept confidential and will be managed in accordance with the below rules:

- All study-related information will be stored securely.
- All CRFs will be identified only by a coded participant number and initials.
- All databases will be password protected.

In the event that a participant revokes authorization to collect or use personal health information, the clinical site retains the ability to use all information collected prior to the revocation of participant authorization. For participants who have revoked authorization to collect or use personal health information, attempts should be made to obtain permission to collect at least vital status (i.e., primary outcome data) at the end of their scheduled study period.

7.4 Protocol Amendments

Any amendments to the study protocol which may affect the conduct of the study or the potential safety of or benefits to participants (e.g., changes to the study objectives, study design, sample size, or study procedures) will require a formal amendment to the protocol. Any protocol amendments will be approved by the Principal Investigators and will require approval by the University of California IRB, the Tanzania NIMR, and the funders (as needed). Administrative changes (e.g., minor corrections or clarifications that have no effect on the way the study is conducted) will not need to undergo a formal amendment process.

7.5 Adverse Event Reporting and Definitions

7.5.1 Adverse Event (AE)

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition (not relevant in this study). AE's will be collected by means of a standard question on the follow-up questionnaire: "Have you developed any new health problems since the previous visit?" AE's will be recorded at every visit. Spontaneously reported AE's and/or observed AE's will be recorded on a separate Adverse Events form with information about (1) date of onset and date of recovery, (2) seriousness, (3) severity and (4) outcome.

7.5.2 Serious Adverse Event (SAE)

A **Serious** Adverse Event is an adverse event occurring during any phase of the study, which fulfills one or more of the following criteria:

1. Results in death;
2. Is immediately life-threatening or requires in-subject hospitalization;

3. Results in persistent or significant disability or incapacity.

The causality of Serious Adverse Events (i.e. the relationship to study treatment) will be assessed by the DSMC, who in completing the relevant REDCAP form must answer 'yes' or 'no' to the question "Is there a reasonable possibility that the event may have been caused by the local Gentamicin injection?"

7.5.3 Safety Monitoring

The following factors should be considered when deciding if there is a "reasonable possibility" that an Adverse Event may have been caused by the investigational product.

- Time course of events and exposure to drug – did the AE occur in a reasonable temporal relationship to the administration of the intervention?
- No alternative cause - the AE cannot be reasonably explained by another etiology such as an underlying disease (not previously present), other drugs, or environmental factors.

There would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course, but there is another more likely cause of the AE.

The subjects will additionally be asked to assess the **severity** of each reported Adverse Event according to the following scale:

Mild	= awareness of sign or symptom, but easily tolerated
Moderate	= discomfort sufficient to cause interference with normal activities
Severe	= incapacitating, with inability to perform normal activities.

Subjects will again be asked about the seriousness and severity of previously reported adverse events at subsequent follow-up visits, in order to track **outcome**.

Adverse Events believed to be secondary to intervention or standard of care with "reasonable probability" will be reviewed at interim analyses, and reported by the DSMC at that time to all required parties.

The Data and Safety Monitoring Committee (DSMC) for the study will consist of will consist of orthopedic surgeon Dr. Marc Tompkins (Minneapolis, MN, USA), emergency medicine physician Dr. Faraja Chiwanga (Dar es Salaam, Tanzania), and health services researcher Nathan O'Hara (Baltimore, MD, USA). Dr. Nathan O'Hara will serve as the committee chair.

7.5.4 Stopping Guidelines

The trial may be terminated for reasons of harm at the judgment of the DSMC. Several endpoints will be examined, including serious adverse events as described in the protocol. While the analysis would consider mal-distribution of predictive factors such as age, it is recognized that ethical considerations require careful considerations of statistical tests as well as qualitative

judgments in the light of experience. Any additional analyses required by the DSMC will be reported as needed.

7.5 Dissemination Policy

At the conclusion of the study there will be a principal manuscript reporting the findings of the feasibility trial primary study endpoints. This data will be used to inform the definitive trial.

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