# BIOMEDICAL RESEARCH PROTOCOL
# UNIVERSITY OF MISSOURI

Project Title: Prospective Randomized Control Trial Comparing Irrisept to Saline Irrigation for the Prevention of Infection After Open Tibia Fractures
IRB Number: 2086908
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## I. Research Objectives/Background

1. Background

Open tibia fractures are at high risk for deep infection (Tornetta et al.). Irrisept is a wound irrigant that has been used to lower infection rates in different wound settings.[6,7] To the investigators' knowledge, there are no robust data showing its effectiveness at lowering infection rates in open tibia fracture management. Therefore, the primary purpose of this study is to determine the effects of Irrisept versus normal saline on deep infection rate following treatment of open tibial fractures. Secondarily, we will perform subcohort analyses to assess the effects of severity grade (type I vs II vs II open) on deep infection rates in open tibia fractures.

2. Research Objectives
    a. Primary
        i. 90-day surgical site infection (SSI) incidence
    b. Secondary
        i. Fracture healing at 6 months
        ii. PROMIS and VAS patient reported outcomes

## II. Drugs/Biologics

1. This study is designed to prospectively compare post-operative infection rates in patients treated for open tibia fractures and wounds irrigated with one of two solutions.
2. Patients will be randomized to one of the two treatments:
    i. Normal Saline
    ii. Irrisept
3. Patients with open tibia fractures will undergo standard operative debridement and appropriate fixation based on the severity and contamination of the fracture.
4. Normal saline is a mix of sodium chloride and sterile water. It has a number of uses in medicine including cleaning wounds.

5. Irrisept is a wound debridement and cleansing lavage system. It contains low concentrations of Chlorhexidine Gluconate (CHG) 0.05% in sterile water. One bottle contains 450 mL 0.05% CHG in sterile water, USP 99.95%. Irrisept is cleared as a Class II Medical Device and an unclassified Combination Product. It can be used as SOC to washout open tibia fractures.

## III. Recruitment Process

1. Recruitment will take place in a private space in the University of Missouri Health System, after identifying a patient over the age of 18 who has an open tibial fracture.
2. Potential participants will be pre-screened initially via medical record/PowerChart/they will then be screened in person to ensure all entry criteria are met.

## IV. Consent Process

1. Consent will be obtained from the potential study subject him or herself. Properly trained and authorized personnel from the research staff or the treatment team will present the study to the potential subject, give them the informed consent to read, review the consent document with the subject and allow them time to consider participation and ask questions. The potential subject will sign and date the informed consent prior to any research activity.

## V. Inclusion/Exclusion Criteria

1. Inclusion
    a. Adult, 18 or over
    b. Open tibia fracture
    c. Able to obtain informed consent from patient
2. Exclusion
    a. Minor, under 18
    b. Pregnancy
    c. Prisoner
    d. Allergic to chlorhexidine gluconate
    e. Unable to provide informed consent

## VI. Number of Subjects

1. We plan to enroll 230 participants (n=230 subjects) (100 subjects per group, 30 screen fails) for a 2-year study. This will allow complete data for at least 200 who will complete the one-year follow-up.
2. This sample size was determined by a pre-study power analysis based on 10% reduction in 90-day SSI incidence with a desired power of 0.8 and alpha set at <0.05.

## VII. Study Procedures/ Design/Treatment Plan

1. Randomization Process
    a. After informed consent is obtained, all patients who meet eligibility criteria will be randomized into one of two groups. Randomization will be achieved by numbering 230 sealed envelopes (115 Irrisept, 115 Normal Saline). There is no blinding to the randomization. It would be difficult to blind the participants or research personnel.
    b. Standard of care at this institution is irrigation with normal saline and debridement.
    c. If randomized to the Irrisept group, patients will be removed from standard of care.
2. Surgery
    a. Patients will be screened and randomized prior to going to the operating room for the initial operative debridement of the open tibia fracture. They will return to the operating room for as many operative debridements as necessary until the definitive fixation surgery is performed.
    b. One group will utilize only Irrisept solution for all open fracture debridements and irrigations, and the other will utilize only normal saline for all debridements and irrigations. Surgical sites that are not the open fracture site should be irrigated with normal saline as per standard of care.
    c. The subjects will undergo standard operative debridement and fixation.
    d. All other components of the management will be standard—antibiotics pre- and postop, surgical debridement, dressings/use of negative pressure wound therapy, etc.
3. Clinical Follow-Up
    a. Standard of Care Standard of Care (SOC)—2 weeks, 6 weeks, 3 months, 6 months and 1 year with tibia radiographs at each visit except the 2-week follow up. Study window will be +/- 2 weeks starting at the 6-week visit.
    b. Tibia radiographs will be collected at each visit per SOC to assess fracture healing as 0-not healed; 1-partially healed; or 2-completely healed.
    c. Deep infection rate as well as wound healing will be assessed. Developing infection would be monitored regardless of the subject's participation in the study.
    d. Patient reported outcomes including PROMIS and VAS pain scores will be collected at each visit per SOC.
    e. Subjects will be monitored at follow-ups for unanticipated events.
4. Subjects will be removed if they do not return to their follow-up visits or do not complete the study specific tasks.
5. Subjects that are removed prematurely or complete the study will continue routine care per physician's standard of care treatment.
6. No specimens will be collected for research purposes.
7. Statistical Analysis – significance set at $p<0.05$.
    a. Primary Outcome Measure: CDC-defined 90-day surgical site infection (SSI) incidence – compared among groups using chi-square test.
    b. Secondary Outcome Measure: Fracture healing at 6 months post-op – compared between groups using a rank sum test.

c. Secondary Outcome Measures: PROMIS and VAS Pain scores – compared between groups using unpaired t-Tests.
d. Secondary Outcome Measure: Multivariate analyses will be used to assess the effects of severity grade (type I vs II vs II open)on deep infection rates in open tibia fractures.

## VIII. Potential Risks/Adverse Events

1. Risks
    a. Risks for breach of confidentiality does exist but will be limited with tight control of data and limited access to the investigators/study team.
    b. There is a minimal increased risk of reaction to chlorhexidine gluconate in the Irrisept treatment group which may include allergic reaction or irritation.
2. Any complications arising from the use of the Irrisept irrigation will be reported to the IRB within 5 days.

## IX. Anticipated Benefits

1. There is no guarantee of direct benefit to study participants.
    a. The data collected will contribute to the orthopaedic knowledge base. We hope it can be implemented to provide improved evidence-based care of these injuries.
    b. Potential benefits include possible lower risk of infection and decreased overall healthcare costs.

## X. Compensation

1. No compensation will be provided to the subjects.

## XI. Costs

1. No research specific costs will be incurred by the research subjects.
2. Standard of care procedures will be billed to the insurance/third party payor/participant.

The costs associated with this study are outlined below:

1. Cost of research support (IRB submission and maintenance, storage and management of study documents, statistical support) = $50,000
2. IRB Fees = $5,500.00 ($2,500 Initial Approval + $1,500.00 Annual Review)
3. Cost of product ($65 x 200 in experimental group) = $ 13,000– Budgeting for 2 bottles of Irrisept solution per case.

## XII. Data Safety Monitoring Plan

1. Patient confidentiality during the course of this study will be protected in compliance with HIPAA requirements as well as the requirements of the University of Missouri Health-Sciences IRB.

2. All subjects will be assigned a study identification number that requires the use of a key in order to decipher a subject's personal identification information. The key will be kept in a secure electronic location, which is password protected. The study identification number will be used to label all paper data collection instruments.
3. All subject information in electronic format will be kept in password-protected storage. All subject information in paper format will be kept in locked cabinets in a secured suite at the Missouri Orthopedic Institute, and otherwise will be archived in a secure storage facility or destroyed.
4. Data will be stored on the Department of Orthopaedic Surgery shared drive and/or PatientIQ, a HIPAA-compliant cloud-based platform that is contracted with the department of orthopaedic surgery.

## XIV. References/Appendices


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