**AWARD NUMBER:** W81XWH-13-1-0492

**TITLE:** The Comparative Efficacy of the Masquelet versus Titanium Mesh Cage Reconstruction Techniques for the Treatment of Large Long Bone Deficiencies

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**REPORT DATE:** Dec 2019

**TYPE OF REPORT:** Final

**PREPARED FOR:** U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

*Form Approved OMB No. 0704-0188*



| **1. REPORT DATE** Dec 2019 | **2. REPORT TYPE** Final | **3. DATES COVERED** 09/30/2013 - 09/29/2019 |
|---|---|---|

**4. TITLE AND SUBTITLE**
The Comparative Efficacy of the Masquelet versus Titanium Mesh Cage Reconstruction Techniques for the Treatment of Large Long Bone Deficiencies

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**
W81XWH-13-1-0492

**5c. PROGRAM ELEMENT NUMBER**

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**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
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**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**
Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**
The study comprises a single-center, randomized, two-arm clinical trial conducted at the Department of Orthopaedic Surgery & Rehabilitation, The University of Texas Medical Branch at Galveston, Texas, with a primary objective to assess and compare the functional outcomes of patients with large segmental bone defects reconstructed with the Masquelet technique (MT) versus the titanium mesh cage technique (CT). The secondary objectives include the radiographic determination of defect healing, and comparative assessment of cost and resource expenditures between the two techniques. From 24 patients with segmental defects presented to our institution throughout the entire trial period, 16 met the study eligibility criteria and were successfully enrolled, and they included 9 MT and 7 CT patients. Within the study period encompassing the last annual report, 7 patients completed the study by reaching the study endpoint, whereas 1 patient's followup was interrupt due to incarceration which precluded continuation in the study, and 1 enrolled patient (CT) received pre-reconstructive defect treatment (infection eradication) but did not meet clinical criteria for the cage reconstructive surgery. Thus, collectively throughout the entire study period, from the total 16 enrolled patients, 11 study subjects (8 MT, 3 CT) completed all the trial followup visits; 1 patient (MT) had incomplete followup, 3 patients (all CT) developed adverse events (recurrence of defect infection) and were removed from the study as reported previously, and 1 patient (CT) was removed due to noncompliance with the study protocol. 1 patient from the Masquelet arm developed unrelated AE and remained in the study. The trial enrollment has been closed, and the participation of all enrolled subjects has ended. The study will be formally closed with IRB before its annual renewal expiration on Jan 14, 2021.

**15. SUBJECT TERMS**
Critical-size bone defects; Segmental bone defect reconstruction; Masquelet technique; Titanium mesh cage technique; Bone grafting.

| **16. SECURITY CLASSIFICATION OF:** U | | | **17. LIMITATION OF ABSTRACT** | **18. NUMBER OF PAGES** | **19a. NAME OF RESPONSIBLE PERSON** USAMRMC |
|---|---|---|---|---|---|
| **a. REPORT** Unclassified | **b. ABSTRACT** Unclassified | **c. THIS PAGE** Unclassified | UU | 19 | **19b. TELEPHONE NUMBER** *(include area code)* |

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## 1. INTRODUCTION:

Segmental bone loss is common sequala of severe extremity trauma in both civilian and the military populations. Motor vehicle accidents, high-energy fractures, gunshot or blast injuries, and also iatrogenic bone resections secondary to infection or tumor are typical etiologies of segmental bone defects. Despite recent advances in limb stabilization and bone healing, achieving healing of bone defect and timely restoring injured limb function remains extremely challenging. Standard treatment options are prolonged, complex, require highly specialized equipment and/or skills, and typically necessitate multiple surgical procedures. Moreover, these treatment modalities are frequently plagued by major complications, rarely restore acceptable limb function, and often culminate with amputation.

This clinical trial was conducted to address these issues by assessing and comparing 2 new bone defect treatment techniques to determine if they were more effective than the standard treatment options for civilian patients. One treatment method tested in the trial—the Masquelet technique—involves two-stage surgery. In the first stage, a cement spacer is applied within the defect to develop a reactive bio-membrane around the defect. This biomembrane is highly vascularized and rich in growth factors, and serves as a biological enclosure for eventual bone graft. The second stage, is performed 6-8 weeks later, and consists of cement spacer removal while preserving the biomembrane, and tightly packing bone graft within the defect enclosed by the biomembrane. The second defect treatment method tested in the trial—the cage technique—was developed by the study principal investigators, and involves a single-stage surgical procedure. In this single-stage defect reconstruction, defect continuity is immediately restored with a cylindrical titanium mesh cage that is tightly packed with bone graft and placed within the defect. Compared to the biomembrane, the cage provides additional biomechanical support, and retains bone graft while permitting its active loading, albeit it lacks the biological characteristics of the biomembrane. Hence, the biomembrane and the cage exhibit distinctive biological and biomechanical properties that provide a unique milieu for bone graft reconstitution and subsequently defect healing. The literature currently suggests that the Masquelet technique can be very effective in achieving bone defect healing; however, our published and unpublished clinical experience with the cage technique has also been quite favorable. To date, there have not been any clinical studies that compare these two defect reconstructive techniques, and this clinical trial aimed at addressing that void.

The study was a single-center, randomized, two-arm, clinical trial conducted in the Department of Orthopaedic Surgery and Rehabilitation, The University of Texas Medical Branch (UTMB) at Galveston, Texas. The trial's primary objective was to assess and compare the functional outcomes of patients with large segmental bone defects of various etiologies reconstructed with the Masquelet technique versus the titanium mesh cage technique, both in combination with bone grafting. The trial's secondary objectives included the radiographic determination of defect healing and the comparative assessment of the etiologies, anatomical locations, severity of bone defects and the characteristics of the patients who present with these clinical entities.

## 2. KEYWORDS:

Critical-size bone defects;
Segmental bone defect reconstruction;
Masquelet technique;
Biomembrane;
Titanium mesh cage technique;
Bone grafting.

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

The study was a single-center, randomized, open-label, two-arm, clinical trial. The overall objective was to compare the clinical efficacy of the Masquelet (Arm I) versus the titanium mesh cage technique (Arm II) technique in combination with autogenous bone graft (RIA harvesting method) (Option A) or allogeneic bone graft composite consisting of cancellous croutons with demineralized bone matrix (DBM) (Option B). By prospectively collecting pertinent preoperative, intraoperative, and postoperative variables, the study was to determine the subjective and objective clinical outcomes for both defect reconstruction modalities and graft options. The enrollment target was 30 patients.

1) The trial's primary objective was to assess and compare the functional outcomes (questionnaires, QALY) of patients with large segmental bone defects of various etiologies reconstructed with the Masquelet technique versus the titanium mesh cage technique, both in combination with bone grafting.
2) The trial's secondary objectives included the radiographic (biplanar radiography, computer tomography) determination of defect healing and the comparative assessment of the characteristics of bone defects and the patients who present with these clinical entities.

These objectives were to be accomplished by addressing the following subaims:

1. Characterize (epidemiologically, medically, statistically) patients who present with segmental bone defects amenable for surgical reconstruction with the Masquelet versus the titanium mesh cage reconstruction technique;

2. Establish the effects of the specific bone defect characteristics (etiology, size, location, adjacent soft tissue status) on the treatment outcome;

3. Determine and compare subjective functional outcomes (pain score, extremity scores, SF36; QALY) between the reconstruction techniques (Arm I vs Arm II) overall and within each graft types (Option A vs Option B);

4. Analyze and compare the merits of selecting the specific graft type (Option A vs Option B) applied within each the Masquelet or titanium mesh cage techniques and their effects on the defect treatment outcome;

5. Develop a quantitative predictive model to improve clinical decision making by delineating which patients are most likely to achieve clinical and quality of life outcomes with the application of the Masquelet versus the titanium mesh cage technique, and by identifying which treatment variables achieve these outcomes;

6. Examine and compare the cost and resource expenditures (ie, length of hospital stay, treatment costs; time to functional recovery) associated with the use of the Masquelet versus the titanium mesh cage technique for treatment of segmental bone deficiency.

The study hypothesis was that the overall clinical efficacy of the titanium mesh cage technique for defect reconstruction is superior to the Masquelet technique, as the former as a single-stage procedure that achieves immediate restoration of the defect continuity while permitting the early functional recovery of the affected extremity and incurring less costs and resources.

- **What was accomplished under these goals?**

Trial subject enrollment and participation:

The enrollment target of the trial was to include and follow 30 eligible patients until they reach the study endpoint, ie 18-month follow-up. Overall, the trial enrollment was sluggish and progressed at the rate slower than initially calculated based on our past yearly presentation of eligible patients with segmental bone defects at our institution. We attempted to enhance the enrollment by obtaining one-year non-cost extension; we also obtained second-year no-cost extension to complete the follow-up of previously enrolled patients.

Over the trial enrollment period, we identified total 33 eligible patients that could potentially be enrolled in the study. Of these patients, 9 were civilian prisoners, and were ineligible for enrollment in the trial. Although we made our several attempts and provided several justifications for including civilian prisoners in the study, our Institutional Review Board (IRB) disallowed us to include these protected individuals as study subjects. Out institution is unique as it provides medical care for the entire Texas Department of Criminal Justice (Texas Prison System) and the civilian prison patients can comprise up to 30% of the musculoskeletal care provided by our Orthopaedic department. Thus, the IRB disallowance significantly compromised our ability to meet the study enrollment goal of 30 patients. An additional 8 non-prison patients were initially screened as eligible for the study but could not be enrolled because they either declined study participation, did not sign informed consent despite initial assurance, or demonstrated signs of potential significant noncompliance with the study protocol, a criterion for study exclusion.

Of 24 eligible defect patients screened, 16 patients have been enrolled in the study and randomized to the Masquelet Arm or the Cage Arm of the trial. Of the 16 enrolled patients, 11 (68%) completed the study endpoints, 1 had partial follow-up and due to being incarceration could not be followed, 3 were removed due to adverse events (AEs), and 1 was removed because noncompliance with the study protocol. The table below depicts the summative patient participation in the trial:

| Trial Arm | Total Trial Subjects Enrolled | Subjects Completed Trial Uneventfully | Subjects with Incomplete Followup | Subjects Removed due to AEs | Subjects Removed due to noncompliance |
|---|---|---|---|---|---|
| Masquelet | 9 | 8 | 1 | 0 | 0 |
| Cage | 7 | 3 | 0 | 3 | 1 |
| **Total:** | **16** | **11** | **1** | **3** | **1** |

The demographic characteristics of trial patients:

The demographic information of 11 patients who completed the trial was as follows: sex: 3♀, 8♂; age: mean 51.2 years, range 34-73 years; ethnicity: 7 Caucasian, 2 African-American; 2 Hispanic. The distribution based on sexes in the Masquelet Arm vs the Cage Arm was 3♀, 5♂ and 0♀, 3♂; whereas mean patient age in the Masquelet Arm vs Cage Arm were 52.7 years and 50 years ($P$=0.7954) (Fig 1A).

The characteristics of the bone defects:

The segmental bone deficiencies in the trial patients exhibited diverse etiologies including: 4 aseptic nonunion with bone loss and excision to healthy margins; 4 infected nonunion with the resection of

the infected bone; 2 osteomyelitis requiring bone resection; 1 segmental defect due to gunshot injury. Anatomical locations of the segmental bone defects included: 3 distal femur, 1 midshaft femur, 1 proximal tibia, 2 midshaft tibia, 1 distal tibia; 2 midshaft humerus, and 1 midshaft ulna. The average defect length was for 6.12 cm for the Masquelet Arm and 5.63 cm for the Cage Arm (*P*=0.6878).

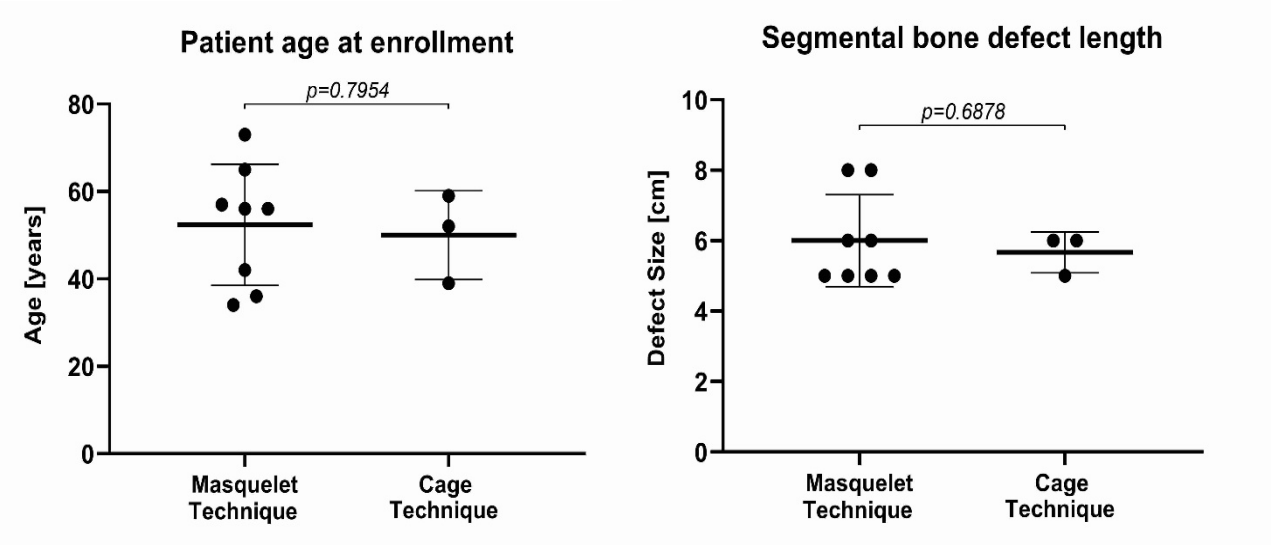


**Figure 1.** The distribution of patients according to age (**A**) and defect size (**B**) in the Masquelet technique versus Cage technique trial arms.

Defect reconstructive surgeries:

No operative issues were encountered during reconstructive surgeries for both the Masquelet and the Cage trials arms. Prior to reconstruction surgery for the Masquelet or the Cage techniques, all trial patients were routinely managed with several standard preparatory non-surgical and surgical procedures to ensure a clean, decontaminated wound with viable residual bone margins and adjacent soft tissue bed. These procedures constituted standard of care and consisted of the following:

- Intravenous and local antibiotics: for patients with bone defect without active infection, prophylactic antibiotics were administered; for patients with infected defects therapeutic systemic broad-spectrum antibiotics were implemented along with the application of local antibiotics eluted from poly(methyl methacrylate) (PMMA) beads or cement spacer.
- Irrigation & debridement: foreign bodies, contaminated, devitalized bone and adjacent soft tissue were removed using serial copious irrigation and surgical debridement; type of irrigating solution, volume, and mode of its application were applied adequately to the degree of wound contamination, infection, and/or necrosis.
- Cultures & histopathology: microbiological evaluation of the defect was routinely performed to confirm its aseptic status and/or infection resolution; histopathological biopsy assessment was done whenever needed.
- Wound closure/coverage: definitive soft tissue closure/coverage occurred when the wound has been adequately decontaminated; a negative-pressure WoundVac was used to facilitate wound closure. Soft tissue coverage and wound healing was required before patient became eligible for bone defect reconstructive surgery.
- Defect stabilization: a cast or spanning external fixation were used to temporary stabilize the defect; definitive defect stabilization was achieved with locking plate constructs or statically locked-intramedullary nails.

In the Masquelet technique, the first stage consisted of excising devitalized and/or infected bone and placing a temporary PMMA spacer in the defect to induce the bio-membrane. The use of definitive stabilization was preferred at this stage, typically consisting of single or dual locked plating. In 1 case used temporary cast stabilization, and temporary external fixation was applied in 2 cases. The second stage of the Masquelet procedure was performed 6-8 weeks later and consisted of PMMA cement removal preservation of the bio-membrane and bone grafting typically consisting of autologous bone graft harvested by means of the Reamer-Irrigator-Aspirator (RIA) system. During this stage, the definitive stabilization was changed from cast to single locked plate in 1 case, from external fixation to dual locked plate in in 2 cases, from initial single locked plate to dual locked plates in 1 case, and remained as single locked plate fixation throughout the entire course of treatment in 8 cases.

In the Cage technique, the cylindrical titanium mesh cage (DePuy Motech, J&J, Warsaw, IN), was used in combination with intramedullary nail in 2 cases or in combination with locked plate in 1 case. The primary choice of bone graft for the Cage technique was an intraoperatively prepared allograft composite consisting of cancellous croutons mixed with demineralized bone matrix (DBM) in volume ratio 3:1.

All patients tolerated both reconstructive surgeries well. The Masquelet patients were permitted protected limb weightbearing/loading between the stage 1 and 2 procedure, whereas the Cage patients were permitted limb weightbearing/loading as tolerated immediately postoperatively.

Bone grafting preference:

There was a strong preference to use RIA-harvested autologous bone (Option A) as a graft choice for the Masquelet technique (7 of 8 cases), although in 1 case allograft was used due to a large defect size and inability to harvest bone graft from either femur using RIA allogeneic cancellous bone with DBM (Option B) was exclusively used for the cage technique (3 of 3 cases). In no case, autologous iliac crest bone graft was used. No problems were encountered with RIA bone graft harvesting or preparing and/or packing the allogenic cancellous crouton-DBM composite.

Functional outcomes:

The summative results of the functional outcome for the trial arms based on SF36 are shown below.

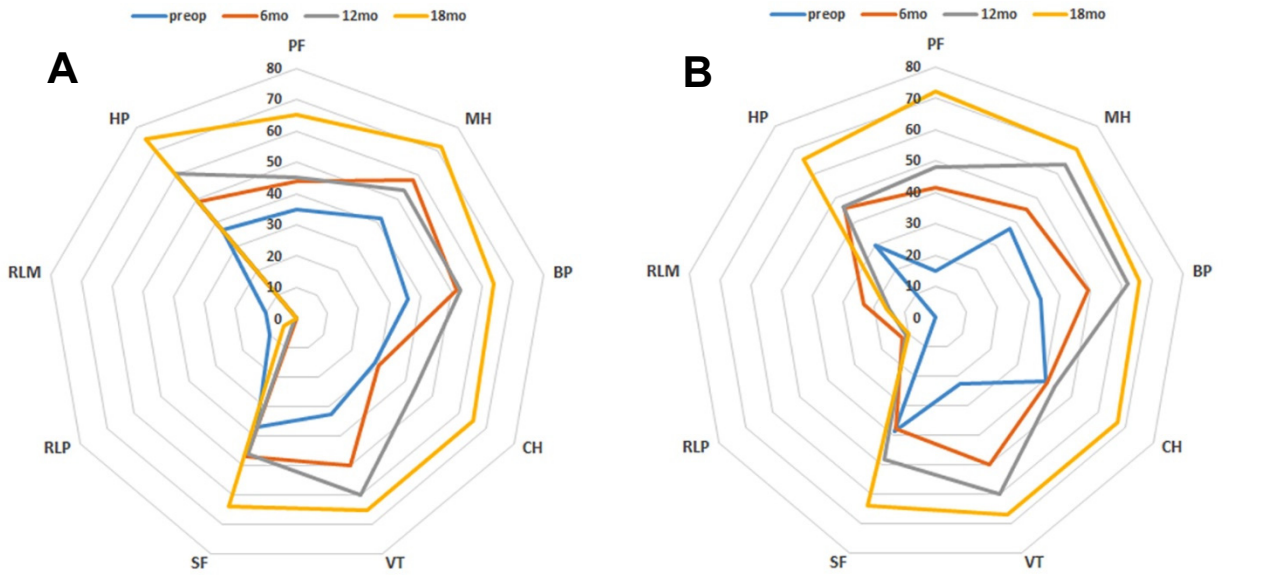


**Figure 2.** Radial plots for the averaged SF36 components before and after treatment with the Masquelet (**A**) versus Cage (**B**) techniques. The followup was collected at preoperatively and at, 6, 12, and 18 months post definitive defect reconstruction. Physical function (PF); Mental health (MH); Social function (SC); Bodily pain (BP); Change in health (CH); Vitality (VT); Role limitation - physical (RLP); Role limitation - mental (RLM); Health perception (HP).

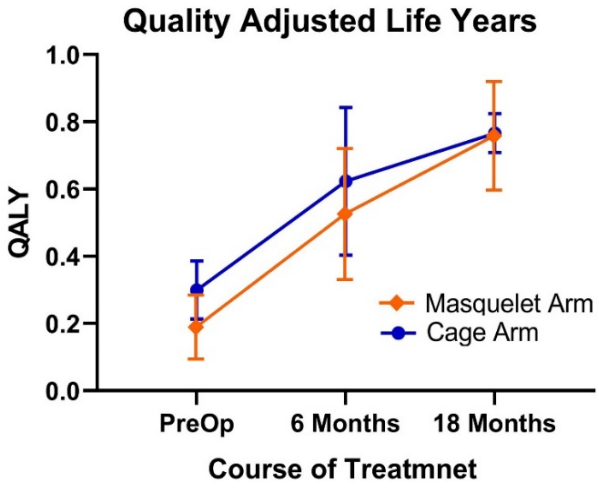


**Figure 3.** An improvement in mean Quality Adjusted Life Years (QALY) calculated from the subjective pain questionnaire throughout the trial followup as a result of bone defect treatment for patients in the Masquelet Arm versus the Cage Arm. QALY values range from 0 to 1 referring to death and perfect health, respectively. There was no statistically significant difference at any time point of the followup between the trial arms.

The nature of trial adverse events (AEs):

Throughout the course of the trial, total 4 AEs were encountered: 3 AE patients required removal from study and in 1 AE patient was allowed to remain and completed the trial. All 3 AEs requiring removal from the trial involved patients randomized to Cage Arm. These AEs involved deep soft tissue infections communicating with the bone defect and/or hardware, thereby mandating a revision surgery with removal of the hardware, including the cage, defect decontamination by serial surgical irrigation and debridement, local antibiotic beads with intravenous antibiotics, before subsequent defect treatment. Based on the microbiology results, a recurrence of infection was in 1 case, and new infection pathogens were identified in 2 cases.

As per protocol of the trial, the 3 AE patients from the Cage Arm met the criteria for removal from further participation in the trial, whereas 1 AE patient from the Masquelet Arm met the criteria to remain in the study. All 4 AEs were timely reported to IRB. It is essential to characterize these AEs, because they impact the trials conclusions. These AEs include:

- AE #1 (Trial patient No.2):

A 36-year old female with a protracted infected nonunion in the proximal tibia treated with resection of the infected bone segment. This patient was randomized to study trial Cage Arm, and received respective Cage Technique in combination with allograft cancellous croutons plus DBM (Option B) as per the trial protocol. The perioperative course was uneventful, and the patient was discharged from hospital. At 2 weeks post defect reconstruction, the patient reported surgical wound healing issues in a telephone conversation. Despite being informed about the serious nature of the concerns and urged to return for immediate evaluation, the patient failed to comply. At 3 weeks post defect surgery, the patient presented to our ER with a wound dehiscence, and was immediately admitted to the hospital. The wound was surgically irrigated and debrided, a WoundVac applied, systemic antibiotic therapy initiated, and the patient was eventually discharged with good prognosis. The patient's failure to attend multiple scheduled clinic visits continued. A social worker reported that the patient was not compliant with the antibiotic therapy, abused illegal substance/drugs, and continued smoking despite being informed about its adverse effects on wound and defect healing. At 2 months post last hospital admission, patient presented to ER again with wound drainage, and extensive skin necrosis over the defect. At that time, the patients requested the limb amputation despite being repeatedly offered the limb salvage options. The patient's postoperative course post amputation was uneventful. The patient wound complication was reported as AE to the UTMB IRB and the DoD, and the patient was withdrawn from the study.

- AE #2 (Trial patient No.4):

A 47-year-old female patient who as per randomization received the Cage reconstruction for a 6.5-cm-long midshaft defect in the humerus presented with an AE just 3 days before completing the final 18-month trial follow-up. At presentation in ER, the patient had pain and swelling in the right upper arm and mild fever. The history and clinical exam were indicative for infection. Right upper arm was swollen, hard on palpation, pink, and warm. Patient reported intermittent fevers over past 3 weeks with temperatures ranging from 101-103. Patient was admitted to hospital, intravenous antibiotics started, and for surgery scheduled for next day. During surgery, posterior triceps splitting through previous incision was made, and a large collection of purulence was encountered at the distal aspect of the incision that tracked deep to the hardware and bone. Cultures were taken and sent to the lab, superficial fat and muscle dissected, and deep fascia was split. Scar tissue was carefully dissected deep, and radial neurovascular bundle was identified and protected throughout the case. The posterior plate was identified and removed, and then the medial plate also removed. Fluoroscopy confirmed removal of hardware. The distal one-third of the cage had achieved full bony incorporation, the proximal one-quarter of the cage has also achieved full bony incorporation with the adjacent bone. The cage could only be resected using oscillating saw to cut through bone at the proximal and distal ends of the cage. The resected cage with its retained bone was removed, and the wound was irrigated with 9 liters of saline. Vancomycin-impregnated beads were placed into the humeral defect, And the wound was closed in layers and dressed with Xeroform, 4x4, soft roll, and a posterior splint. The patient was taken to the PACU in stable condition. At this admission patients tested positive for the presence of illegal street drugs (amphetamine). Due to the nature of the AE patients has been removed from participation in the study.

- AE #3 (Trial patient No.11):

A 48-old male patients randomized to the Cage Arm for the treatment of his 5-cm-long midshaft tibial bone defect, presented to the clinic at 6-months post reconstructive surgery with foul-smelling drainage from the original surgical wound. Prior to these symptoms, patient's postsurgical course had been uneventful and wound had been completely healed. At presentation, patient had no fever, lower extremity motor function grossly intact, and sensation to light touch in deep peroneal, superficial peroneal, tibial, sural, and saphenous distributions was preserved. There were palpable pedal pulses. A 5x3 cm wound opening over the left anteromedial tibia was noted with exposed hardware and bone and a positive foul odor without gross purulence. Subject was admitted to the hospital and underwent surgical exploration. During surgery necrotic and contaminated tissue was removed, tibial debridement and jet lavage using saline was performed, and the tibial hardware (including the cage) was removed. The bone defect was packed with antibiotic beads, and subsequently a WoundVac was placed to drain the surgical site and enhance wound healing, and the subject was discharged from hospital. The nature of this AE met the exclusion criteria for the study, and consequently the subject was removed from study participation.

- AE #4 (Trial patient No.14):

A 57-year-old male randomized to the Masquelet Arm, had completed both stages of the Masquelet defect reconstruction when he presented to the ER with fever with maximum reported temperature of 104. The patient reported having low-grade fevers at home and also mentioned that he accidentally removed an intravenous PICC line and re-introduced it back to the vein by himself. Patient also reported removing his splint at home, but denied numbness/tingling distally in this left arm. The study physician evaluated the patient that day in the clinic where further diagnostic tests were ordered. The patient's chest computed tomography imaging demonstrated multiple scattered lesions in lungs which were diagnosed as possibly being septic emboli. The PICC line was removed and blood cultures obtained. There were no signs of surgical site infection at this time. Patient was discharged from the

ER and his culture results confirmed a gram-negative bacteremia with *Enterobacter*. Patient was called immediately contacted and admitted to the hospital where he was treated with IV antibiotics. The patient's bacteremia symptoms resolved, and he was discharged on oral antibiotics and with a good prognosis. This AE has been recorded, but as per trial protocol it did not affect the patient's participation in the study. The patient completed the trial uneventfully after this event.

All 3 AEs that met criteria for removal from the trial occurred in patient in the Cage Arm, and they all were infections. The first 2 AE patients developed new pathogens, likely attributable lack of compliance with the treatment, physician's recommendations, poor hygiene, and drug abuse. The 3rd AE involved a recurrence of the original infection with subsequent development of draining sinus. Based on the nature of these 3 AEs, it can be concluded that the Cage technique poses higher risk of infection compared to the Masquelet technique, especially in wounds with prior contamination. This, thereby, mandates the rigorous establishment of an infection-free surgical/bone defect site before large bony defects may be amenable for definitive single-stage reconstruction. This may involve a prolonged preparative antibiotic treatment combined with aggressive excision of infected, necrotic, devascularized bone, particularly if applied for the treatment of infected nonunion or osteomyelitis. Furthermore, despite being a single-stage surgery and seemingly more appropriate for less compliant patient, the Cage technique is can be considered only for a patient who can strictly complies with the treatment, and has no additional risks factors for developing infection.

Overall Conclusions:

Although the trial did not meet the initial enrollment goal, and is underpowered, the results indicate that the Masquelet technique outperformed the Cage technique in our patient population in terms of the rate of complications, particularly infection. Of 8 patients enrolled to the Masquelet Arm, none developed an AE related to the defect treatment; whereas 3 of 7 (43%) patients enrolled in the Cage Arm developed AEs pertinent to the defect treatment and mandating removal from the study.

The trial results indicate that the Cage technique poses higher risk of infection compared to the Masquelet technique, and may be best suited for a lower-risk patient population (eg, tumor resections, aseptic defects). In the post-traumatic patient, the Cage technique, more so than the Masquelet requires an infection-free host and bone defect soft tissue site amenable for definitive reconstruction. Extended periods of local and intravenous antibiotic administration are essential in addition to the aggressive debridement of infected, necrotic, or devascularized bone if the Cage technique is applied for post infectious indications, such as septic nonunion or osteomyelitis.

The trial results suggest that both the Masquelet and Cage defect reconstructions can effectively restore the continuity of segmental bone loss in long bones. All patients who successfully completed the trial in both trial arms demonstrated very good clinical outcome. However, patient compliance is critical in achieving satisfactory results. Because the Masquelet technique comprises of 2-stage surgical procedure, patient's compliance with treatment can be more adequately assessed prior to definitive bone grafting compared to the 1-stage Cage procedure. Unlike the latter, definitive reconstruction (second surgery) can be postponed or averted in case of any suspicion of poor compliance.

This trial was a single-center clinical research, and despite actively seeking referrals and familiarizing the regional medical community about the trial, the eligible patient accrual for the trial was below the target and significantly lower than anticipated. Considering the complexity of the trial and potentially high rate of screen failures, here 33% (8 of 24), this particular research is perhaps best suited as a multicenter trial with more patients and treating physicians involved. The recent improvements in trauma care, effective guidelines for antibiotic therapy and wound management resulted in lowering

the numbers of the patients presenting with infected nonunions requiring iatrogenic resections and defect reconstructions. This further emphasizes the need for a concerted multicenter effort.

This trial compared the Masquelet vs Cage techniques; however, a recently published study (Gavaskar et al. Injury 2020) demonstrated merits of combining both these 2 techniques into one to further enhance clinical outcome. Thus, in future prospective trials to establish the optimal bone defect reconstruction options, a combined staged Masquelet-Cage technique may warrant strong consideration.

Examples of cases from both trial arms:

**The Masquelet Arm patient**: A 73-year-old male with a chronic infected nonunion/defect in the tibial mid-diaphysis was enrolled to the study and randomized to the Masquelet technique. The patient received the 2-stage Masquelet reconstructive surgery for bone defect in combination with allograft-DBM composite (Option B). The RIA graft harvesting (typical for the Masquelet technique) was not used because of an ipsilateral knee prosthesis. The patient completed all study followup visits and demonstrated defect healing with very good radiographic and functional outcomes.

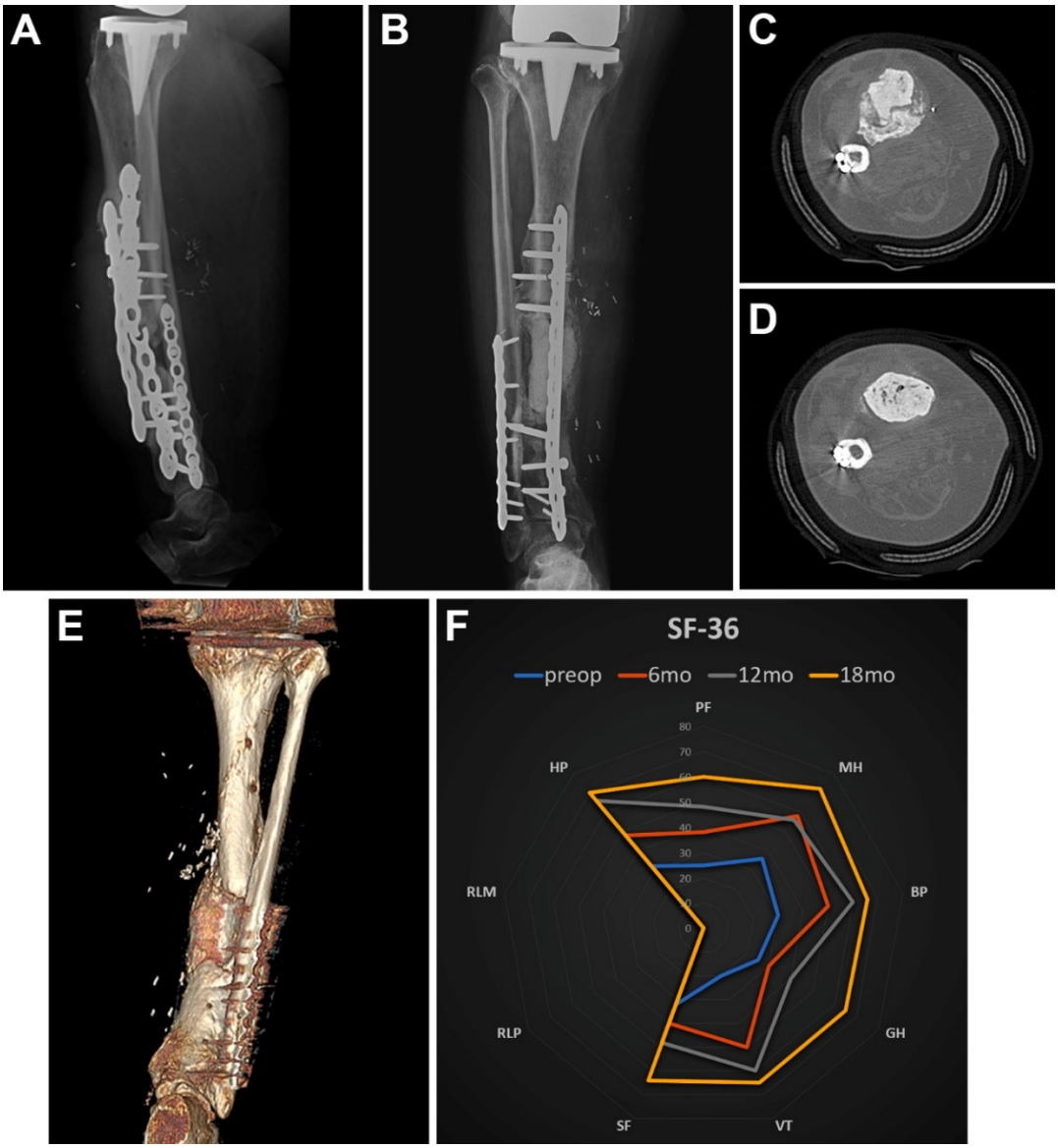


**Figure 4.** A tibial mid-diaphyseal infected nonunion with hardware failure (**A**) was treated with 2-stage Masquelet technique with allograft, and locking plate stabilization. The graft consolidation was evident of plane radiography (**B**), cross-sectional CT (**C,D**), and 3D CT reconstruction (**E**). Progressive increase in overall functional status was obtained as indicated by scores from SF36 (**F**).

**The Cage Arm patient:** A 59-year-old male presented with infected nonunion in the tibia as a result of open fracture. The patient was enrolled into the study and randomized to the Cage technique for defect reconstruction in combination with allograft-DBM composite. The patient completed all the study follow-up visits, and demonstrated uneventful defect healing as evidenced by plain radiography, computed tomography, and functional assessments.

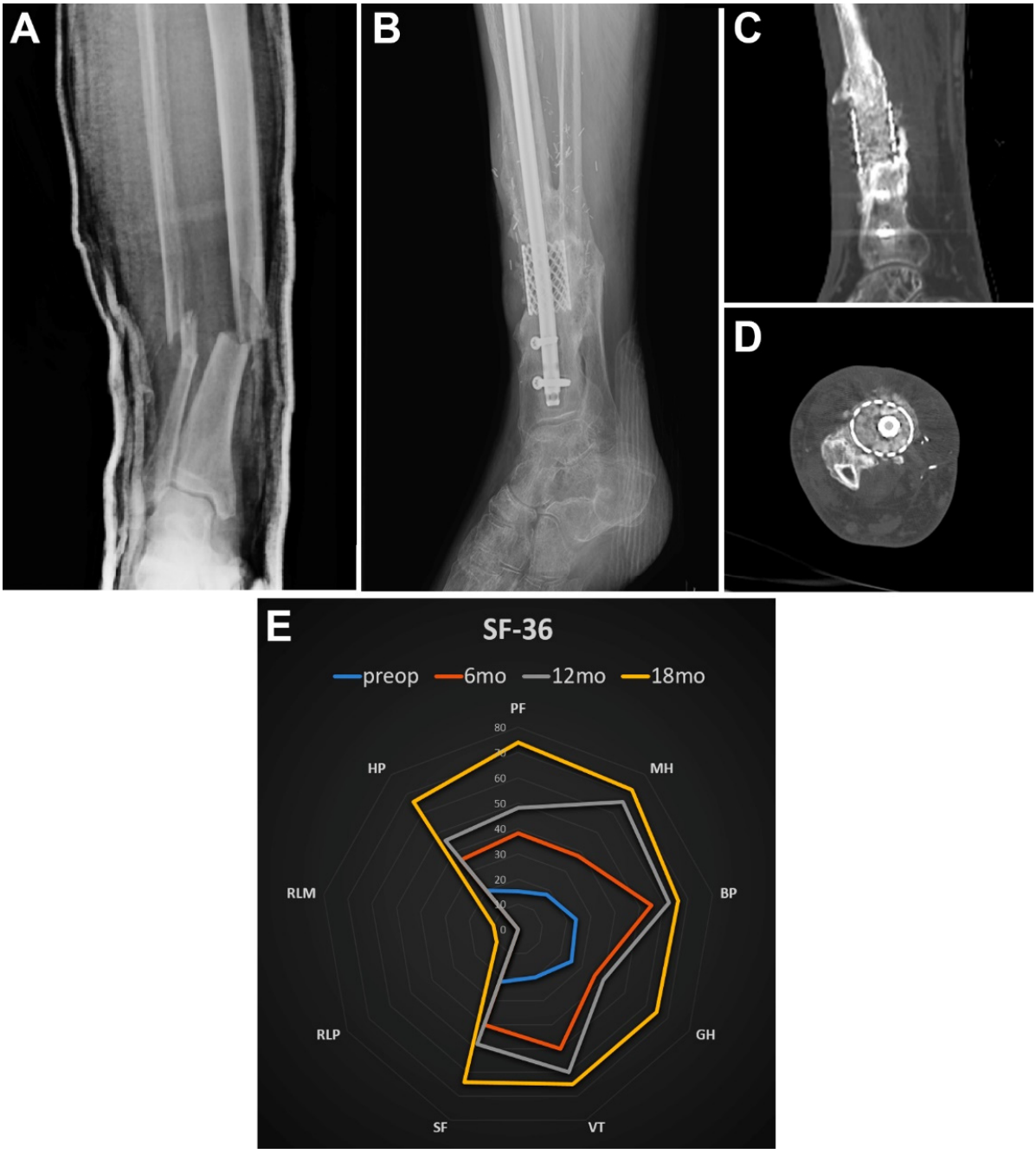


**Figure 5.** A chronic infected nonunion following Grade IIIB open tibia fracture (**A**). The excised infected bone produced segmental defect treated with a cylindrical titanium cage in combination with allograft-DBM, and stabilized with an IM nail. The defect healing progressed uneventfully to union as indicated by plane radiography at 18 months (**B**). The cage was filled with new bone (**C,D**). The patient's functional outcome as per SF36 has progressively improved throughout the followup (**E**).

- **What opportunities for training and professional development has the project provided?**

  The treatment of segmental bone deficiencies in the extremities poses formidable challenges. Conventional treatment options, such as massive cancellous none grafting, cortical bone grafts, or bone transport have well appreciated limitations such as unreliable outcomes, protracted treatment, the risk of pain medication dependency, and limited limb mobility and/or function. Vascularized bone grafting is a viable option but is technically very demanding, requires special skills and equipment, and requires along period of protected weightbearing or limb loading until the graft has hypertrophied. Thus, the conventional options produce highly unreliable and/or unsatisfactory results that frequently culminate in amputation. Recently, two new limb preservation techniques for treatment of large segmental bone defects have emerged. One is the Masquelet technique—a two-stage surgery, which relies on inducing a bio- membrane around the defects by placing the PMMA cement; 6-8 weeks later, the surgical cement is removed and the defect is bone grafted. The other technique, the Cage technique, was developed by the study PIs— and involves the placement of a titanium mesh cage packed with bone graft that immediately restores defect continuity in a single surgical setting. The current literature and PIs' clinical experience indicate that both of these methods can be effective; however, in many institutions these new bone defect reconstructive methods are not routinely practiced and taught.

  This clinical trial, albeit limited in scope as a single-center effort, exposed many orthopedic residents, fellows, and faculty in our institution to these to novel bone defect treatment techniques (in addition to Trauma surgeons, Plastic surgeons, Radiologists, Infectious Disease specialists, Pathologists, Physiatrists and Physical Therapists). By assisting in the surgeries as part of the trial, our orthopedic trainees, fellows, and faculty colleagues learned first-hand all steps of these 2 surgical techniques and gained skills and knowledge to practice them by themselves beside the trial. Furthermore, whenever the trial cases appeared in our M&M teaching conferences, we, as PIs, took the opportunity to further present these two techniques and discuss them in details with our trainees and faculty.

- **How were the results disseminated to communities of interest?**

  We disseminated our knowledge and experience with the new bone defect reconstruction techniques in our local medical community and beyond. We presented the merits of these treatment options and familiarized the audience with our clinical trial in the following regional and national conferences/symposia:

  - Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. MD Anderson Grand Round Talk, Houston, TX, on Nov 7, 2013.
  - Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. UTMB Grand Rounds, Houston, TX, on Nov 26, 2013.
  - Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. Baylor College of Medicine Grand Rounds, Houston, TX, on Oct 10, 2014.

- Lindsey RW & Gugala Z. A DoD-UTMB Clinical Trial Determining the Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. UTMB Monthly Conference, Victory Lakes, TX, on Jan 21, 2015.
- Lindsey RW. Managing post-traumatic femoral bone defects. The UCSF Annual International Orthopaedic Trauma Course. San Francisco, CA. April 28, 2016.
- Lindsey RW, Gugala Z. New Horizons: Experience with the Bone Cage. The 26th Annual Meeting of the Baltimore Limb Deformity Course: Masters of Disaster Managing Osteomyelitis in the 21st Century. Baltimore, MD. August 25, 2016.
- Lindsey RW. Titanium Cages: How We Can Enhance Their Success. The Annual Meeting of the Orthopaedic Trauma Association. National Harbor, MD. October 5-8, 2016.

We are currently in the process of preparing a manuscript for submission to a peer-reviewed journal.

- **What do you plan to do during the next reporting period to accomplish the goals?**

  Nothing to report—this is the final report.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

  This research generates knowledge product on how to treat segmental bone defects. It also outlines the benefits and drawback of both of these new defect reconstructive methods. It further indicates, that potentially combining the Masquelet with the cage technique may offer added benefits. Such approach has very recently been used by the PIs (unpublished data) with very promising results and also by others authors (Gavaskar AS et al. A load-sharing nail-cage construct may improve outcome after induced membrane technique for segmental tibial defects. Injury 2020;51:510-515) with adherence to the he PIs' cage method. This offers exciting future continuation of the work that is subject of this trial, and can potentially significantly impact on the management of segmental bone loss for both civilian and military patients.

- **What was the impact on other disciplines?**

  This clinical trial can have potential impact of biomaterial sciences, bioengineering, and implant design, specifically to enable fabrication of custom, defect-specific, designed for the individual patient, 3D-printed titanium cages to be used in conjunction with bioactive/biologic components such growth factors or tissue-engineered bone graft substitutes. Furthermore, the research identifies a need for a novel cement spacers with a better elution kinetics and more effectively inducing the biomembrane. Finally, these studies further emphasize relevant molecular biology and cellular preclinical research to understand the mechanisms of bone formation in the microenvironment compromised by infection, and effective means to augment bone and soft tissue healing.

- **What was the impact on technology transfer?**

  Nothing to Report.

- **What was the impact on society beyond science and technology?**

  Nothing to Report.

5. **CHANGES/PROBLEMS:**

We experienced problems with reaching the enrollment goal for our trial—30 patients. We have screened 24 eligible patients, enrolled 16, and only 11 patients successfully completed the trial. Prior to initiation of the trial, we reviewed the historical incidence of yearly presentation of patients with segmental bone defects at our institution and calculated the enrollment target of 30 patients as very feasible to achieve within the trial period. Our inability to enroll civilian prisoners (9 patients) due to the IRB disallowance, additionally compromised our ability to reach the trial enrollment goal.

The recent COVID-19 pandemic caused a delay in submitting this final report; this has been communicated to DoD and received an approval.

There have been no changes to the originally approved study protocol or in direction of this research.

- **Changes in approach and reasons for change**

  Nothing to report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Nothing to report.

- **Changes that had a significant impact on expenditures**

  Nothing to report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  - There have been no protocol deviations or protocol violations throughout the trial.
  - There were 4 adverse events (AEs); they all have been timely reported to IRB and DoD.
  - There were no laps in trial approvals. The annual approvals were timely and systematically obtained from IRB for the throughout the consecutive trial periods as follows:

    - May 15, 2013 – Apr 26, 2014
    - Apr 13, 2014 – Mar 28, 2015
    - Mar 23, 2015 – Mar 13, 2016
    - Mar 11, 2016 – Mar 11, 2017
    - Mar 09, 2017 – Mar 09, 2018
    - Jan 26, 2018 – Jan 25, 2019
    - Jan 13, 2019 – Jan 14, 2020

    The current annual IRB approval of the trial expires on Jan 14, 2021; the study will be administratively closed before the final renewal expires.

- **Significant changes in use or care of human subjects**

  Nothing to report.

- **Significant changes in use or care of vertebrate animals.**

  Nothing to report.

- **Significant changes in use of biohazards and/or select agents**

  Nothing to report.

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**
  - **Journal publications.**

    Nothing to report.

  - **Books or other non-periodical, one-time publications.**

    Nothing to report.

  - **Other publications, conference papers, and presentations.**

    Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. MD Anderson Grand Round Talk, Houston, TX, on Nov 7, 2013.

    Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. UTMB Grand Rounds, Houston, TX, on Nov 26, 2013.

    Lindsey RW & Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. Baylor College of Medicine Grand Rounds, Houston, TX, on Oct 10, 2014.

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    Lindsey RW. Managing post-traumatic femoral bone defects. The UCSF Annual International Orthopaedic Trauma Course. San Francisco, CA. April 28, 2016.

    Lindsey RW, Gugala Z. New Horizons: Experience with the Bone Cage. The 26th Annual Meeting of the Baltimore Limb Deformity Course: Masters of Disaster Managing Osteomyelitis in the 21st Century. Baltimore, MD. August 25, 2016.

    Lindsey RW. Titanium Cages: How We Can Enhance Their Success. The Annual Meeting of the Orthopaedic Trauma Association. National Harbor, MD. October 5-8, 2016.

- **Website(s) or other Internet site(s)**

  https://www.clinicaltrials.gov/ct2/show/NCT02015390

- **Technologies or techniques**
  Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Nothing to report.

- **Other Products**
  Nothing to report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

| | |
|---|---|
| Name: | *Zbigniew Gugala, MD,PhD* |
| Project Role: | *PI* |
| Researcher Identifier | *ORCID: 0000-0003-2331-7660* |
| Nearest person month worked: | *72* |
| Contribution to Project: | *Execution of the trial and supervision of the trial team* |
| Funding Support: | |

| | |
|---|---|
| Name: | *Ronald W. Lindsey, MD* |
| Project Role: | *Co-PI* |
| Researcher Identifier | *ORCID: 0000-0002-3223-0252* |
| Nearest person month worked: | *60* |
| Contribution to Project: | *Orthopedic Surgeon* |
| Funding Support: | |

| | |
|---|---|
| Name: | *Nikoletta Carayannopoulos, MD* |
| Project Role: | *Co-I* |
| Researcher Identifier | *-* |
| Nearest person month worked: | *36* |
| Contribution to Project: | *Orthopedic Surgeon* |
| Funding Support: | |

| | |
|---|---|
| Name: | *Rickeedah Gitrey, MS* |
| Project Role: | *Clinical Coordinator* |
| Researcher Identifier | *-* |

| | |
|---|---|
| Nearest person month worked: | *36* |
| Contribution to Project: | *Coordinating scheduling, documenting* |
| Funding Support: | |

| | |
|---|---|
| Name: | *Safee Ahmed, MS* |
| Project Role: | *Clinical Coordinator* |
| Researcher Identifier | - |
| Nearest person month worked: | *36* |
| Contribution to Project: | *Coordinating scheduling, documenting* |
| Funding Support: | |

| | |
|---|---|
| Name: | *Kristopher Jennings, PhD* |
| Project Role: | *Collabolator* |
| Researcher Identifier | - |
| Nearest person month worked: | *60* |
| Contribution to Project: | *Biostatistical planning and analyses* |
| Funding Support: | |

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Nothing to report.

- **What other organizations were involved as partners?**

  Nothing to report.

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:**

  Not applicable.

- **QUAD CHART:**

## The Comparative Efficacy of the Masquelet versus Titanium Mesh Cage Reconstruction Techniques for the Treatment of Large Long Bone Deficiencies

OR120128

**PI:** Zbigniew Gugala,MD,PhD **Org:** University of Texas Medical Branch **Award Amount:** $840,485

**Study Aims**

- Establish the effects of the specific patient and bone defect characteristics on the treatment outcome;
- Determine and compare clinical efficacies of the reconstruction techniques (Arm I vs Arm II);
- Establish the merits of using specific graft type (Option A vs Option B) within and across each study arms;
- Develop a quantitative predictive model to improve clinical decision making;
- Assess and compare the cost-effectiveness and resource expenditures incurred by the specific treatment selection.

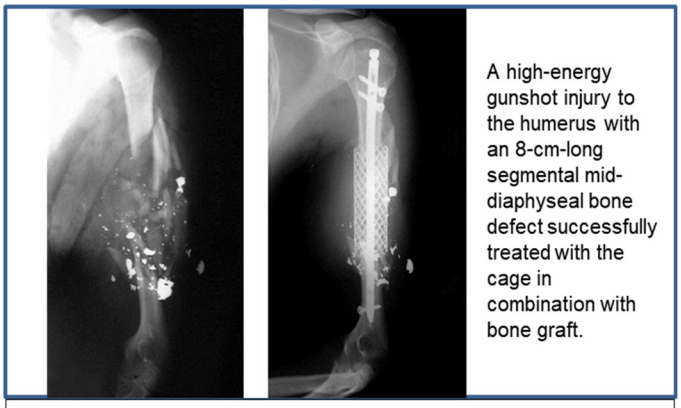
**Approach**

Single-center, multi-site, two-arm, randomized clinical trial. Thirty patients with segmental bone deficiency as a result of trauma, gunshot, iatrogenic resection due to infection, nonunion, or neoplasm will be enrolled and randomized to receive either the Masquelet (Arm I) or the CTMC as definitive defect treatment (Arm II). Bone graft selection will include either RIA-harvested autograft (Option A) or allograft croutons-DBM composite (Option B). Patients will be followed up to18 months.

### Timeline and Cost

| Activities / CY | 14 | 15 | 16 | 17 | NCE 18 | NCE 19 |
|---|---|---|---|---|---|---|
| IRB, CRFs, Patient Recruitment, Enrollment, Defect Surgery | | | | | | |
| Continued Enrollment, Defect Surgery, Patient Followup | | | | | | |
| Continued Recruitment, Surgery, Followup, Initial Data Analysis | | | | | | |
| Final Followup & Final Data Analysis, Presentation, Publication | | | | | | |
| **Estimated Budget ($K)** | **$212** | **$202** | **$216** | **$210** | **$37** | **$0** |

**Updated:** Jul 22, 2020



A high-energy gunshot injury to the humerus with an 8-cm-long segmental mid-diaphyseal bone defect successfully treated with the cage in combination with bone graft.

**Goals/Milestones:**

**CY13 Goal** – Acquiring all study approvals, designing CRFs, building patients database, recruitment, and enrollment of study subjects. Defect surgery, initial evaluation & follow-up.

**CY14 Goal** – Continuing recruitment/enrollment, defect surgery, patient follow-up study monitoring, reporting.

**CY15 Goal** – Continuing recruitment/enrollment, defect surgery, Patient follow-up, monitoring, initial data analysis, reporting.

**CY16 Goal** – Continuing recruitment/enrollment, defect surgery, Patient follow-up, monitoring, initial data analysis,

**CY17 Goal** – Completing patient follow-up, thorough data analysis, interpretation, presenting, and publishing.

**Comments/Challenges/Issues/Concerns**

- No cost extension granted for Ys 2018, 2019; the trial is closed.

**Budget Expenditure to Date**

Projected Expenditure: 840,485

Actual Expenditure: 840,485

9. **APPENDICES:**

Nothing to report.