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

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THE STUDY PROTOCOL

The proposed study is a single-center, prospective, two-arm, randomized clinical trial. The study is conducted and coordinated by the University of Texas Medical Branch (UTMB) and its affiliated John Sealy Hospital; Galveston, TX as a study site. Patients who present to these hospitals with a traumatic segmental bone loss (high-energy trauma, gunshot injury) or a medical condition (infection, nonunion, tumor) which requires iatrogenic segmental bone resection will be enrolled into the study after inclusion/exclusion criteria have been met and signed informed consent obtained. Routine patient management (standard of care) will be performed prior to the Masquelet or the cylindrical titanium mesh cage (CTMC) reconstruction in accordance with the patient's bone defect characteristics and overall health status. Post enrollment, the study subjects will be randomized into either the Masquelet (Arm I) or the CTMC defect treatment technique (Arm II). All aspects of pre-, intra-, and postoperative patient and defect management will strictly adhere to the IRB-approved study research protocol. Within each study arm, two distinct options of bone graft will be available for use in combination with the Masquelet or the CTMC defect reconstruction, and they include: autogenous RIAharvested bone graft (Option A) obtained from reaming of either the intramedullary femoral or tibial canal, or fresh-frozen cancellous allograft in combination with demineralized bone matrix (Option B). The decision on graft option is made by the patient following an in-depth review by a treating physician (study PI).

STUDY DESIGN:

The proposed randomized clinical trial aims to determine the comparative efficacy of the Masquelet versus the CTMC technique in combination with RIA-harvested autogenous bone graft or allogeneic cancellous bone croutons-DBM composite as reconstructive modalities of segmental bone defects. The Masquelet technique can be regarded as a new standard treatment option in the orthopedic practice as frequently indicated and supported by the literature. The CTMC technique will be considered as experimental defect treatment option, which utilizes the titanium mesh cage in an innovative manner, although originally approved and cleared by the FDA for such use. Because both the Masquelet and the CTMC treatment techniques have potentially similar clinical indications, randomization will be performed to assign the enrolled patients to a specific treatment group (Arm I or Arm II) to ensure bias-free selection process. The choice of graft type (Option A versus Option B) to be used in combination with either the Masquelet or the CTMC technique will be nonrandomized and made by the enrolled patient following an in-depth review and explanation of each graft option by the treating physician. Since many patients have subjective preference as to whether their own bone or bone from the bone bank should be used as graft material, such a study design will not exclude the eligible patients because of that preference, thereby enhancing study accrual and enrollment. Furthermore, the merits and justification supporting the specific graft selection will be treated as significant covariate in the subsequent analysis of the treatment outcome and resource expenditure.

Treatment Arm Randomization

The assignment of patients to treatment groups (Arm I versus Arm II) will be done using the nQuery Advisor random assignment generation algorithm. The software options in nQuery allow for random block sizes to be generated, allowing for a better guarantee of balance while making the assignment largely unpredictable. Our biostatistician will use the nQuery software to generate 30 random numbers linked to 15 Arm I and 15 Arm II

labels. An additional random sequence listing 10 Arm I and Arm II will be created as a backup in case of randomization irregularities. The Arm I and Arm II sequence will be used to consecutively designate the specific treatment arm for the enrolled patients. Randomized treatment arm assignments will be kept in sealed opaque envelopes and will not be known to the treating orthopedic surgeons (R.W.L.; N.L.C.) and the patients prior to the enrollment. The PI (Z.G.) and the study coordinating team will maintain a randomization confidential throughout the study. After a patient has been successfully enrolled to the study, the envelope will be opened and the treatment arm designation revealed. The defect treatment will follow exactly as revealed. Any randomization irregularities (ie, lost envelopes, envelopes opened but not used, numbers inadvertently skipped) will be reordered and reported to the institutional IRB.

Course of Action

Patients who present to the study site with a segmental defect or medical condition (nonunion, infection, neoplasm) to be treated with a segmental bone resection will be routinely admitted and the PI (Z.G.) notified. The patient and his/her medical condition will be reviewed in accordance with the study inclusion/exclusion criteria. If eligible, the patient will be enrolled in the study subsequent to discussing and explaining in detail the study protocol and obtaining a signed informed consent. The patient will then be randomized and assigned into one of the two treatment groups, ie the Masquelet or the CTMC technique (Arm I or Arm II). Next, following a thorough explanation of the defect graft options by the treating physician, the patients will select the graft type to be used with the randomly assigned treatment arm. The pre-operative data will be collected as per the study protocol, and necessary imaging/studies obtained. The required routine (standard of care) surgical procedure(s) preceding the defect treatment technique will be performed. Only if and when the defect is suitable for reconstruction, the first of two-stage surgery of the Masquelet technique (cement spacer application) or the single-stage CTMC procedure will be performed. The select orthopedic surgeons specializing in the Masquelet technique (N.L.C.) or CTMC technique (R.W.L.) will perform the specific defect reconstructive surgery (both cement spacer and grafting stages of the Masquelet or the entire single-stage cage with grafting of the CTMC technique) for all of the enrolled patients to ensure the consistency in the defect reconstruction and the postoperative patient management. For the Masquelet technique, there will be a routine 6-8 week period between the two stages of defect management. The type of definitive defect stabilization (eg, IM nail, platescrew construct) will be selected by the treating orthopedic surgeon. All the intraoperative data will be collected by the PI (Z.G.) or study staff. The patient's post-surgical course will be performed as mandated by the technique of defect treatment. For the Masquelet, the limb weight bearing protocol will be strictly followed depending on the consolidation status of the graft. For patients undergoing the CTMC postoperative course, weight bearing will be permitted as tolerated. Subjective data (patient questionnaire), objective functional data (outcome scores), and imaging data will be collected pre-, and post-defect reconstruction as designated in the study protocol (pre-hospital, inpatient period, and outpatient follow-up visits at 2 weeks, 6 weeks, 12 weeks, and 18 weeks post defect reconstruction).

Throughout the entire post-operative study period (18 months), the patient's status will be monitored for complications and adverse events. If a complication or adverse events occurs, they will be reviewed by the PIs, the study staff, and key personnel and reported to the UTMB IRB according to regulatory and institutional policies. In addition, the study documents will be monitored by the UTMB's Research Services, Monitoring and Quality Assurance department for Clinical Research at 3-month-intervals. For the duration of the study, the PIs will routinely meet with the study coordinating staff to discuss the study progress, review the enrolled patients, and discuss all complications and/or adverse events as they occur. At 6 month intervals the PIs will meet with the study's biostatistician to perform preliminary statistical analysis of the collected data. The investigators will use

these meetings to make adjustments in the course of the study in case of enrollment issues and/or other logistic problems occur.

Study Variables

All study preoperative, intraoperative and postoperative variables will be recorded to construct a database of patients presenting with segmental bone defects and treated with the Masquelet or the CTMC technique in combination of auto- or allograft.

Preoperative variables are defined as all the patients- and their health-related data that are collected prior to the Masquelet or the CTMC reconstructive procedure (to include surgeries performed prior to the first stage of the Masquelet or the index CTMC surgical procedure). Preoperative variables to be collected will include:

- Patient (baseline):
  A) Demographics (age, gender, ethnicity; social functioning/background);
  B) Overall health status;
  C) Risk factors (tobacco, alcohol, recreational drugs);
  D) Co-morbidities
  E) Concomitant medications (past 60 days prior to enrollment)
  F) Past (last 10 years) medical history
- Defect:
  A) Etiology:
     Traumatic: Systemic and specific extremity injury characteristics to include Injury Severity Score (ISS) (Baker 1974); Gustilo-Anderson classification (Gustilo 1976) for open fractures, gunshot injury characteristics, type of firearm, bullet/missile retention; nature and extent of blast injury, limb neurovascular status.
     Iatrogenic: Specific diagnosis, details on disease (infection, tumor) course and history; type of nonunion (hyper-, oligo-, atrophic, septic).
  B) Characteristics: Location, size, degree of contamination, and adjacent soft tissue status. Imaging: plain radiography, CT (in select cases).
- Affected Limb Function:
  A) Ambulation (passive, active, range of motion);
  B) Pain;
  C) Weight bearing status;
  D) Functional assessment (DASH for the upper extremity, and AAOS Lower Limb Core Scale for the lower extremity).
- Pre-Masquelet or pre-CTMC treatment:
  A) Nature, number, timing of all treatment interventions, specifically data on all surgical procedures performed prior to the defect reconstruction;
  B) Provisional defect stabilization;
  C) Soft tissue coverage (type of closure/flap, timing).

Intraoperative variables are defined as those that are recorded during the first and the second stage of the Masquelet or the index CTMC reconstructive procedure. These include data pertaining to:

- Iatrogenic resection: the defect size, geometry, location; determination of healthy margins; (if segmental resection is performed on the same operative setting); quality of soft tissue envelope.
- Masquelet: 1st stage: spacer cement type, volume, if with antibiotics (types/concentration), *in situ* or *ex vivo* cement polymerization.
  2nd stage: time between the stages; quality and patency of biomembrane; technique of the cement spacer extraction.
- CTMC: cage type, manufacturer, dimensions (diameter, length).
- Bone graft:
  A) RIA-harvested autograft (Option A): location, technique, volume, timing;
  B) Allograft-DBM (Option B): allograft tracking number; allograft/DBM provider; volume; cancellous croutons to DBM ratio;
- Definitive defect fixation: IM nail, plate-screws type, manufacturer, dimensions.

- Reconstruction Surgery:
  A) Quality of reduction, alignment;
  B) Type of definitive stabilization;
  C) Intraoperative plain radiography;
  D) Tourniquet time;
  E) Fluoroscopy time;
  F) Surgery time;
  G) Intraoperative blood loss / transfusions;
- Complications and/or adverse events encountered intraoperatively.

Postoperative variables are defined as those that are recorded after the second stage of the Masquelet or the index CTMC defect reconstructive procedure. They include clinical examination, imaging, pain and limb function assessment, and the overall treatment outcome (questionnaires). The followup data are collected at hospital discharge, at 2 weeks, 6 weeks, 3 months, 6 months, 12 months and 18 months post defect reconstruction surgery. Postoperative complications and/or adverse events will be documented and reported.

Defect Healing Assessment

The radiographic determination of defect healing will consist of a 5-grade scale (ranging from no healing to completely healed) in quarter defect length increments (ie, 0%, 24%, 50%, 75%, 100% defect healed). The radiographic review will be conducted by the PIs and 2 independent reviewers. Inter- and intrarater agreement will be calculated for the final determination of the defect healing status.

CT imaging will be performed routinely at 12 months post defect reconstruction surgery to visualize the new bone formation/graft reconstitution within the defect using two- and three-dimensional reconstructions. Spatial determination of new bone formation will be carried out in relation to the defect, the hardware, and the local

anatomic landmarks. The quantitative (bone volume) and qualitative (mineral density) will be calculated following a metallic hardware (cage, nail, plate-screws) subtraction algorithm.

Questionnaires

Questionnaires will be used in the study as outcome instruments for defining the safety characteristics of the enrolled subjects; determining the longitudinal impact on health changes, function and satisfaction; delineating the effectiveness of the Masquelet versus CTMC technique of defect reconstruction; developing of specific evidence-based medicine clinical pathways and guidelines.

The following questionnaires will be used in the study as outcome instruments:
Brief Pain Inventory Short Form (Cleeland 1994);

- Disabilities of the Arm, Shoulder, and Hand (DASH) for the upper extremity (Hudak 1996);
- Lower Limb Core Scale (LLCS) for the lower extremity (Johanson 2004);
- Medical Outcomes Survey Short-Form 36 (SF-36) (Ware 1996);
- Time Trade-Off to assess Quality-Adjusted Life Years (QALY) (Torrance 1987).

All these questionnaires have been validated as valuable outcome measure instruments. Furthermore, they are endorsed by the American Academy of Orthopaedic Surgeon as recommended reliable and valid tools in the assessment of musculoskeletal treatment outcome. The enrolled patients will complete the questionnaires at the initial, midcourse, and final follow-up visits. The time burden to complete the questionnaires is approximately 30 minutes.

Statistical Methodology

Descriptive statistics will be used to analyze the collected data specifically to:

- characterize the patient with segmental bone deficiency; estimate the proportion of healing with/without complications; cross-compare the recorded variables.

Paired Student t-test will be used to test the effects of the Masquelet versus the CTMC defect reconstruction on the outcome measures.

Analysis of covariance (ANCOVA) will be used for pair-wise comparison within the two treatment arms (graft Option A vs. Option B).

A mixed model for repeated measures will be conducted to evaluate:

- the effect of the Masquelet versus CTMC defect reconstruction on the outcome measures, adjusting for patient demographics and clinical characteristics;
- the effect of the specific defect characteristics (etiology, size, location, adjacent soft tissue involvement, etc) on the treatment outcome;
- the possible interaction effects between treatment and defect characteristics.

Multiple models will be used in case the proposed sample size would not have enough power to produce an accurate predictive model which accounts for all possible morbidities and interactions. Simple models using modern penalty function techniques (lasso, elastic net, boosted trees, etc.) to control model complexity should provide a useful initial predictive tool for each clinical and quality of life outcome.

Both receiver operating curve (ROC) analysis and clinical judgment will be used in determining the optimal clinical indications and timing for defect reconstitution with the definitive defect reconstruction using the Masquelet versus the CTMC technique.

Sample Size Justification

Based on the data from the PIs' preliminary clinical series of 20 patients, it can be assumed that 75% of patients with segmental bone defects reconstructed with the CTMC technique will heal without complications. In the present study we propose to enroll and follow-up on 30 patients throughout 4 years of the clinical trial duration. This sample size of 30 is largely determined by clinical feasibility. For the sample size 30, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.134 from the observed proportion for an expected proportion of 0.75.

Our past experience with prospectively investigating 20 patients with traumatic segmental defects presented to our institution (single site) within 2.5-year period suggests that the 30 patients to be enrolled in the proposed study within the anticipated time frame is very feasible considering broader inclusion criteria.

Data Analysis

Prospectively collecting pertinent pre-, intra-, and postoperative study variables will establish a database of patients with segmental bone defects reconstructed with CTMC in combination with bone graft of bone graft substitute. A series of multivariate models will be constructed to model sizeable complex interactions between the patient, defect etiology and characteristics, process of care variables and surgical outcomes. Specific analyses will be performed to address the following questions:

- What are the characteristics of the patients who present with segmental bone deficiency warranting surgical reconstruction that achieve superior functional and quality of life outcomes when treated with the Masquelet versus the CTMC technique?
- What is the nature of a segmental bone defect and its related variables that determine superior outcomes after the Masquelet versus the CTMC reconstruction?
- What are the aspects of pre-, intra-, and postoperative care that differ for patients who:
  A) achieve poor outcomes;
  B) sustain treatment related complications;
  C) incur resource usage well in access of the average?

Resources Expenditure and Cost-Effectiveness Analysis

The treatment cost calculations for patients treated with the Masquelet (Arm I) or the CTMC technique (Arm II) in combination with auto- (Option A) or allograft (Option B) will include the length of hospital stay, overall treatment cost, and the comparative cost-efficiency assessment. The clinical characteristics of the study arms will be reported with means and standard deviations, frequencies, or percents, when appropriate. All analyses of outcomes will be performed both as "intent-to-treat" and as "efficacy." Average charges in the two groups will be compared with a Student t-test or Wilcoxon rank sum test. The progression of defect healing based on imaging evaluation (using both qualitative and quantitative measures) and functional recovery assessment (both subjective questionnaire, and objective outcome scores) will be compared with the log-rank test and proportional hazards model. Frequencies of repeat surgical intervention and complications will be compared with chi-square tests. Because there are two designated expert surgeons who will each be performing a single study arm, consistency could be expected within each treatment arm as it relates to the specifics of the surgical intervention and the post-surgical course of patient management.

The standard economic evaluation approach to assessing the difference between the two defect treatment arms is to construct a comparative cost-effectiveness ratio for each arm. This will include determining the incremental

progress in defect healing and/or functional restoration in relation to the treatment time and finally to the costs and/or resources allocated to achieve that. Our expectation is that clinical outcomes will favor the CTMC technique because of its single stage surgery, shorter treatment time, efficacious defect healing, and early unrestricted functional restoration. It is important to emphasize that the primary determination in the study is to establish whether applying one of the treatment arms versus the other is associated with clinically- and/or statistically-significant improvement in outcome, and secondarily assess the time, cost, and resources that enabled that improvement. Both the estimated outcome and cost differences can exhibit some variation, however, accounting for uncertainty in estimates has become an important component of economic evaluation. Derived from the joint distribution of costs and effects, cost-effectiveness acceptability curves (CEACs) will be established to summarize the uncertainty in cost-effectiveness estimations. This is particularly important if the study arm is found to be cost-effective rather than cost-saving.

HUMAN SUBJECT RECRUITMENT AND SAFETY PROCEDURES

Patients with segmental long bone defects or conditions requiring a segmental bone resection will be reviewed for study eligibility as per protocol inclusion/exclusion criteria. Potential study participants will be identified after they are admitted to the UTMB John Sealy Hospital; Galveston, TX. The selection of this hospital can offer access to a diverse patient population not only in terms of the nature of the study medical problem (segmental bone defects) but also demographic, social, health care accessibility characteristics. The hospital specializes in distinct areas of orthopeadic care and thereby can provide eligible patients with bone defects of various etiologies (posttraumatic vs iatrogenic resections; acute vs chronic) and anatomic locations (lower- and upper extremity). The diverse patients recruited to the study will represent study subjects with different treatment outcome expectations, thereby reinforcing the study's validity as being more representative of the entire US society. This type of approach will also promote equity in social status by permitting all patients to incur the burdens as well as the benefits of the segmental bone defect treatment. The recruitment of patients eligible for the study will be equitable; there will be no limitations regarding age (except for skeletal maturity), gender, race, ethnic and cultural factors.

Because of the unique nature of the defect etiology (trauma, iatrogenic resections due to nonunion, infection, tumor), and to avoid unanticipated delays and/or a slow accrual in study subject enrollment, an active physician's referral program will be implemented.

Study Inclusion Criteria:

All eligible patients will be screened and enrolled as they present for treatment without consideration of race, gender, or cultural/religious consideration.

- Male or female;
- Skeletal maturity (defined by the absence of epiphyseal plate and/or age $\geq$ 18 years); All ethnic backgrounds;
- Presence of segmental bone defect requiring surgical reconstruction with at least one of the following etiologies:

A) traumatic segmental bone defect that warrants surgical reconstruction;

B) acquired bony nonunion (not congenital) treatable by segmental resection and reconstruction; C) local osteomyelitis (dormant or active) treatable by segmental bone resection and reconstruction;
D) localized, nonmalignant tumor with involvement of bone diaphysis treatable by segmental bone resection and reconstruction.
E) suffiecint comprehension of the English language to understand the consenting process and study procedures

Protected Eligible Patient Groups

- Eligible patient has a mental disorder or medical condition/s that reduces his/her ability to make an informed decision and has the consent of his/her legal guardian and/or health care surrogate; are you going to remove this bullet? There is a different explanation under vulnerable pop below.
- Eligible patient is illiterate and has a non-party observer present during the reading of the informed consent AND the non-party observer witnesses the subject's consent to participate;

Defect Eligibility Characteristics

To be eligible for the study the study inclusion criteria mandates that a patient presents with a segmental bone deficiency requiring surgical reconstruction.

- Size: Typical size of a defect that warrants surgical reconstruction (beyond functional limb shortening) eligible for the study inclusion is:

A) greater than 5 cm in length for the humerus;
B) greater than 2 cm in length for the tibia, femur, radius, ulna.

- Etiology: The eligible defects can be of the following etiology:
    A) traumatic, typically as a result of high-energy injury or gunshot injury;
    B) iatrogenic, resection of nonunion, infection, or tumor.
- Onset/Duration: Eligible defects can be defined as:
    A) acute (time from the injury or resection less than 2 weeks);
    B) subacute (time from the injury or resection greater than 2 weeks but less than 3 months);
    C) chronic (time from injury or resection greater than 3 months).

According to this designation, typical acute defects include those that are reconstructed during or immediately after irrigation and debridement. Typical subacute defects are those that require staged soft tissue coverage prior to the reconstruction. All defects that result from previously failed treatment are designated as chronic, and those typically comprise nonunions and infections.

- Location: The eligible defect must be located in proximal, mid or distal shaft of the following major extremity long bones:
    A) Humerus;
    B) Radius/Ulna; C) Femur;
D) Tibia.

- Microbiology: The sterility of the defect needs to be confirmed using routine microbiology (wound cultures) and/or pathology histologic evaluation. Infected defects will undergo routine treatment which will consist of systemic and locally applied antibiotics (antibiotic-impregnated cement spacer or beads) until wound sterility is confirmed by microbiology/pathology evaluation.
- Adjacent soft tissue status: Eligible defects must have adjacent soft tissue that is suitable for surgical reconstruction. Thereby, wound coverage can be achieved following defect reconstruction by either the closure of viable wound margins or the placement of soft tissue flaps (local or free). Wound coverage may be done as a staged surgical procedure (soft tissue coverage typically as much as 6 weeks prior to definitive defect reconstruction), or as a single stage procedure (performed at the same time as the definitive defect surgical procedure).

Study Exclusion Criteria:

- Non-segmental defects (e.g., defect in continuity involving only single cortex);
- Inability or contraindications to achieve stabilization with an IM nail;
- Insufficient defect size (humerus defects less than 5 cm; femur or tibia defect less than 2 cm in length);
- Extremity unsuitable for salvage;
- Patients with inadequate neuro-vascular status;
- Defect and/or soft tissue status ineligible for surgical reconstruction;
- Ipsilateral extremity defect (e.g., tibia and femur ipsilateral defects);
- Skeletal immaturity (open growth plate and/or age less than 18 years);
- Known allergic reaction to titanium implants;
- Disseminated osteomyelitis throughout the bone;
- Active systemic infection at time of surgery;
- Congenital / genetic etiology of nonunion (congenital pseudoarthrosis, osteogenesis imperfecta, etc.);
- Women who are pregnant or nursing;
- Women who intend to become pregnant during the study follow-up (i.e., 2 years);
- Disseminated and/or nonresectable malignant tumor involving bone;
- Patients with active compartment syndrome;
- Prisoners;
- Patients considered as non-compliant with medical and follow up care;
- Patients using narcotics, abusing prescription drugs (within last 2 years);
- Patients with alcohol abuse;
- Patients deemed incapable of following instructions pertaining to post operative care due to mental or medical condition;
- Patients deemed ineligible due to medico-social concerns.

Study Termination or End Point:

Consideration for termination of the subject participation in the study after the subject has been enrolled and/or study end point includes:

- Intraoperative determination of need for surgical procedure outside the study scope or protocol;
- Identifying any valid exclusion criterion after the subject's enrollment;
- Secondary procedure disrupting or preventing implementation of either the Masquelet or the CTMC defect reconstruction technique as in the study protocol;
- Evidence of infection or neoplasm recurrence post defect reconstruction;
- Evidence of vascular compromise in the affected extremity resulting in secondary intervention affecting healing;
- Subject declines continued participation;
- Subject is non-compliant with follow up care and instructions;
- Termination for any reason deemed mandatory by the PIs;
- Defect is completely healed before the end of the follow-up (i.e., 24 months); Subject becomes pregnant before the defect reconstructive surgery; Subject completes the study.

Subject Recruitment

Patients who present to the UTMB hospital with a traumatic segmental defect or a medical condition (nonunion, infection, neoplasm) to be treated with segmental bone resection will be recruited either prior to or following hospital admission. The PI (Z.G.) will be notified by the admitting physician. The patient and his/her medical conditions will be reviewed in accordance with the study inclusion/exclusion criteria. If eligible, patients will be approached to discuss their participation in the study.

The study discussion will include an explanation of the study objectives; the voluntary nature of the research; study requirements and/or compliance; randomization into one of the study treatment arms, termination and end points; reviewing both the Masquelet and the CTMC surgical defect reconstructive procedures; the alternative defect treatment options; the selection of autogenous RIA-harvested bone graft or allogeneic bone in combination with DBM, the study risks and benefits, the confidentiality of the subject's information, medical records and study-related documents, the potential costs to the patient and/or the patients insurance (standard of care), the costs covered through study funding; the contact persons/agencies for questions.

Obtaining Signed Informed Consent

Informed consent will be signed by all eligible patients in the presence of a witness prior to any study activity. The independent witness must be a person who is not a member of the research team. The independent witness will countersign the informed consent indicating the patient's verbalized understanding of study and the patient's intent to be enrolled in the study.

The study PI will be responsible for explaining the study, answering questions, and obtaining informed consent from the eligible patients. Eligible patients will be recruited after their presentation/admission to the hospital study site. Informed consent will be obtained after procedures determining study eligibility. Eligible patients will be offered privacy and time to make the decision regarding their participation in the study; they will be encouraged to discuss this decision with their family members or others of their choice.

The eligible patients' health status will be reviewed to confirm that his/her cognitive capacity (eg, no mental alteration due to administration of any mind-altering substances such as tranquilizers, conscious sedation or anesthesia, brain injury, stress/life situations, or volunteer age) permits obtaining full conscious (not under drug influence) consent for participation in the study. In cases where such mental alteration exists, the recruitment will

be postponed; these patients will be reassessed, and when appropriate, approached again for recruitment when conscious informed consent can be obtained.

No waiver of the informed consent for study enrollment is sought. Minors are ineligible for participation as per the study inclusion/exclusion criteria.

Subject Reimbursement for Study-Related Expenses

Reimbursement for time, travel, parking, and meals for each completed study visit is provided.

In addition and due to time commitment for 2 week, 12 month and the 18 month visits, subjects will receive additional reimbursement.

Total reimbursement is $700. The reimbursement will be only for competed study visits. UTMB Clincard, which is a debit card with funds loaded will be issued as follows: $200 at visit 1 (at 2 weeks); $50 at visit 2 (at 6 weeks); $50 at visit 3 (at 3 months); $50 at visit 4 (at 6 months); $150 at visit 5 (at 12 months), and $200 at the final visit 6 (at 18 months). When a study visit is completed, funds will be approved and loaded onto the card. The funds will be available within 48 hours. One card will be issued for the duration of the subject participation. All information is stored in the Clincard system will be kept and handled in a secure fashion and will be deleted from system once the study has been completed and the funds on the card have been all used.

INTERVENTIONS AS THE STUDY RESERCH:

They study intervention that are performed outside the standard of care and solely for research include:

1. Randomization to one of the two study arms.
2. Collection of pre-, intra-, and postoperative data.
3. Completing outcome questionnaires

INTERVENTIONS AS THE STANDARD OF CARE:

Procedures Preceding the Defect Reconstruction

Prior to segmental defect reconstruction with either the Masquelet or the CTMC technique, several preparatory non-surgical and surgical procedures must be performed to ensure a clean, de-contaminated wound with viable residual bone margins and adjacent soft tissue bed. These procedures constitute the current standard of care for all defect reconstruction modalities, and consist of the following:

- *Antibiotics:* For patients with segmental bone defect without active infection, prophylactic antibiotics will be administered; for patients with infected defects therapeutic systemic broad-spectrum antibiotics are implemented along with the application of local antibiotics eluted from cement beads or spacer.
- *Irrigation & debridement:* Foreign bodies, contaminated, devitalized bone and adjacent soft tissue will be removed using serial surgical irrigation and debridement. Type of irrigating solution, volume, and mode of its application should be adequate to the degree of wound contamination, infection, necrosis.
- *Cultures & biopsy:* Microbiological evaluation of the defect will be performed to confirm its aseptic status and/or infection resolution. Histopathological biopsy assessment is done for neoplasms as a part of routine diagnosis.

- *Wound closure/coverage*: Definitive soft tissue closure/coverage will occur when the wound has been adequately de-contaminated of all foreign body, infection and contamination.
- *Temporary defect stabilization:* Provisional plaster splint (acute defect reconstruction) or spanning external fixation (delayed defect reconstruction) will be used to temporary stabilize the defect.

RIA Autogenous Bone Graft Harvesting (Option A)

For RIA procedure of autograft harvesting from the femur, a bump will be placed under the ipsilateral hemipelvis similar to the position for a free leg femoral nail. The narrowest section of the femur or tibia is templated on anterior–posterior (AP) and lateral fluoroscopy to determine the intramedullary canal size. The reamer size then selected will be approximately 1-1.5 mm larger in diameter than the measured canal size. The tip of greater trochanter is used as an entry postal under the guidance from biplanar fluoroscopy. The standard anterior proximal tibia entry portal typically employed for IM tibial nailing will be used for tibia RIA autograft harvesting. A 13-mm cannulated drill bit is used to create the entry site, after a ball-tip guide wire inserted advanced down into IM canal. The RIA system (Synthes US; West Chester, Pennsylvania) is assembled to harvest bone graft. This includes attaching a properly sized reamer head, connecting 3-5 liter saline bag to the RIA irrigation port, establishing suction to the RIA aspiration port and connecting a suitable graft collecting container with a filter with 500 μm pore size (The Screen Trap; Biomet, Warsaw, IN). Gravity flow and vacuum suction are used to maintain irrigation flow. The IM canal is subsequently reamed with the properly sized reamer in an alternating forward-and-backward pattern. The femur will undergo 2 to 4 RIA reamer IM passes depending on the size of the defect to be grafted. For larger defects, autograft harvesting volume can be increased by advancing the guide wire sequentially into both the lateral and then the medial femur condyles to enable graft harvesting from both locations. After RIA reaming is completed, the trap is disconnected and bone graft collected. The harvested bone graft then is immediately packed into the defect with defect biomembrane or into the cylindrical titanium mesh cage. Care is taken to apply the RIA autograft into the reconstructed defect in a timely manner in order to maximize it biological healing potential.

The Masquelet Technique (Arm I) for Bone Defect Reconstruction

Overall Concept and Rationale

In a seminal paper (Masquelet 2000), Masquelet described a two-stage technique for the treatment of large segmental bone defects that involves the induction of a biomembrane about a PMMA cement spacer within the defect and, following cement removal, autogenous bone grafting of the defect while preserving the biomembrane. The typical time interval between the two stages is 6-8 weeks (Masquelet 2010). The biomembrane not only assists in retaining the bone graft, but serves as a rich source of vascular supply and growth factors which constitute an excellent biological milieu for the graft to consolidate and heal the defect being (Pelissier 2004).

Description of the Masquelet Technique

In the first stage of the Masquelet technique, the defect is meticulously irrigated and debrided by removing all contaminants, debris, and necrotic or devitalized tissue. At this stage the limb anatomical alignment is also restored and provisionally stabilized, the defect is assessed/templated for its size and geometry to determine the most suitable type of definitive stabilization. At the second stage procedure the temporary stabilization is removed and converted to either a plate-screw construct or an IM nail as the definitive mode of defect fixation. Definitive soft tissue coverage is also typically accomplished at this stage after defect sterility has been confirmed by microbiology and/or other pathology studies. The PMMA cement is prepared with a volume slightly exceeding

the confines of the defect to eventually accommodate the effective volume of the graft in the second stage. If there is an ongoing concern for infection (i.e. a Gustilo Grade II or III open fracture; acute/chronic osteomyelitis), the PMMA cement is combined with vancomycin and/or tobramycin at the therapeutic concentrations for local antibiotic delivery. Because of exothermic polymerization of the PMMA, adjacent nerve and vessels must be retracted/protected until the cement cures and reaches body temperature. PMMA volumetric expansion during polymerization should be taken into consideration to adequately adjust the volume of cement at the defect; an excessive PMMA spacer might cause problems maintaining an intact biomembrane during its removal.

The second, bone grafting stage is typically formed at 6-8 weeks post PMMA cement spacer placement. The defect is exposed through the same incision used for cement placement. When a plate-screw is used for defect stabilization, the biomembrane is typically formed around the plate and the cement spacer. The biomembrane surrounding the spacer is incised longitudinally along the plate border leaving a margin sufficient enough to permit re-approximation/closure of the biomembrane after bone grafting is performed. Once exposed, the cement spacer is removed en bloc or in small fragments using a rongeur and/or drilling. Although it is imperative that all of the cement spacer and its fragments are removed, exceptional care is taken to avoid violating the biomembrane surrounding the cement apart from the longitudinal incision. After this is accomplished, the biomembrane lodge is irrigated copiously to ensure removal of all spacer debris. In case of autogenous bone grafting using RIA, the fomoral and/or tibial IM canal(s) are reamed to harvest sufficient bone graft. If the harvested RIA graft is insufficient, it can be supplemented with autogenous iliac crest bone. The bone graft is packed into the biomembrane void immediately post harvesting and should fill the entire cavity. If allograft is used, a graft composite consisting of freeze-dried cancellous croutons mixed with demineralized bone matrix (DBM will be prepared using Grafton putty (Osteotech, Eatontown, NJ) at a volume ratio approximately 3-to-1, respectively. The allograft composite is fragmented with a rongeur to a consistent fragment size, and then packed to the biomembrane lodge filling it tightly. The biomembrane lodge should be filled entirely, but not overpacked to cause problems with biomembrane closure. Once the lodge is packed, the biomembrane is carefully closed with absorbable suture, followed by wound closure. It is imperative to obtain haemostatic wound closure.

Postoperative Course

The patient is permitted immediate passive motion using a continuous passive motion (CPM) device when appropriate. Pain control is implemented as a routine. Physical therapy will be initiated at 2 days post defect reconstruction. Lower extremity weight bearing will be gradually applied as tolerated at about 6 weeks after the bone grafting stage of the Masquelet procedure. Full weigh bearing without restrictions is resumed depending upon the graft consolidation, defect healing, and the patency of the defect/extremity stabilization.

<u>The CTMC Technique (Arm II) for Segmental Defect Reconstruction</u>

Overall Concept and Rationale

We have demonstrated the biological and biomechanical merits of the CTMC technique in the treatment of large segmental bone defects (Cobos 2000; Lindsey 2004). Compared to the Masquelet technique, the CTMC technique is a single-stage surgical procedure that immediately restores limb anatomy and alignment, and provides limb stability sufficient enough for early, unrestricted mobilization while permitting bone and soft tissue healing. Moreover, this reconstruction method pioneers the concept of a “bio-logic implant” (the highly synergistic combination of stabilizing implants cage/nail or cage/plate) with a biologically-active graft) (Gugala 2007).

Description of the CTMC Technique

The indications for the CTMC technique include any clinical setting of a segmental bone defect that warrants surgical reconstruction. The CTMC technique can be adapted to long bone segmental lesions in the diaphysis, metaphysis-diaphysis segments, or transarticular joint fusion. Prerequisites for the procedure are an aseptic wound with a healthy soft tissue envelope, adequate bone quality and anatomy that can accommodate either an IM nail or plate/screw fixation, and CTMC augmentation with bone graft or graft substitute. The CTMC technique is not only a viable alternative to all standard primary treatment modalities, but it can be used as a salvage procedure for any failed standard treatment modalities. The CTMC technique is particularly indicated for patients who cannot, for whatever reason, tolerate multiple surgical procedures.

To ensure the suitability of the defect for reconstruction, the surrounding soft tissues are meticulously debrided to de-contaminate the wound. After an aseptic wound has been achieved, the length and diameter of the bone defect is determined, and a titanium mesh cage of appropriate size is selected. For diaphyseal defect reconstructions, the diameter of the mesh cage should be slightly larger than the adjacent cortex to allow the host bone to allow it to axially load the graft material contained within the mesh. Metaphyseal and transarticular reconstructions are achieved with the largest diameter cage that can be accommodated at the site. In these cases, the span of the cage should be equivalent to the length of the defect, as opposed to the diaphysis where the cage length should be 1-2 cm longer than the defect to allow for cage overlap with the host bone. The strength of the cage can be reinforced with rings placed along the inner perimeter of the implant and secured with screws.

After a trial fit of the mesh in the defect confirms its adequate length, the mesh is tightly packed with bone graft. Two graft options are offered as per study protocol: autogenous RIA-harvested bone graft (Option A), or allogeneic cancellous bone graft from combined with DBM (Option B).

In cases of IM nail fixation, prior to cage placement into the wound, a guide wire is inserted longitudinally through the middle of the packed cage, and the cage/allograft construct is sequentially reamed to a diameter which will ultimately permit the passage of an IM nail. The CTMC-graft construct is then positioned in the defect/wound, and, under image intensification, a guide wire is passed through the host bone medullary canal, across the cage-graft, and seated at an appropriate distance within the distal bone fragment. Additional bone graft is placed along the periphery of the cage adjacent to muscles, and at the cage-host bone junction. Following wound closure, either direct or by soft tissue flap, the host bone/implanted CTMC-graft construct is reamed *in situ*. A titanium IM nail of adequate size and length is inserted in a standard fashion into the medullary canal and across the cage. The limb is manually compressed axially over the cage prior to statically interlocking the nail.

In cases that are not stabilized with an IM nail, the cage is packed with bone graft, placed in the defect, and stabilized with a titanium locking plate and screws. The locking plate screws should achieve fixation in at least six cortices on each side of the defect. While applying the plate and screws, host bone compression is obtained across the graft within the cage. The plate should lie on the host bone cortex in a manner that it allows space for the cage that overrides the edges of the defect.

Postoperative Course

Immediately post CTMC defect reconstructive surgery, the subject is permitted to mobilize the operated limb as tolerated. In lower extremity defects, a CPM device can be applied until the patient can become ambulatory. Pain control is implemented as per routine. Standard physical therapy will be initiated at 2 days post defect reconstruction. No restrictions will be placed upon the mobilization and/or weight bearing of the operated limb. Weight bearing upon the reconstructed extremity is permitted as tolerated. The time needed to achieve full weight bearing post-surgery will be documented.

Study Follow-up

Surgery and immediate postoperative care will be conducted at the UTMB affiliated hospitals as the study sites, while the postoperative care after hospital discharge can be performed in the hospital's or UTMB outpatient clinics.

Follow up care will be conducted through the PI's (R.W.L.) practice at the intervals considered as routine. This routine follow-up is conducted at 2 weeks, 6 weeks, 3 months, 6 months, 12 months, and 18 months, with a plus or minus 5 day window for each visit. Additional unscheduled visits may be needed to evaluate healing and will be at the discretion of the PIs. These additional visits will be monitored by the research team to determine interval changes impacting protocol events, radiographic evidence of healing or failure and adverse events.

DRUGS / DEVICES / IMPLANTS:

Medications

No specific medications related to the Masquelet or the CTMC defect reconstruction procedures will be used. The use of prophylactic or therapeutic medications (e.g., antibiotics, anticoagulants, etc.) in the pre-, intra- or postoperative course of defect treatment will follow the standards of care for routine segmental bone defect management irrespective of the defect reconstructive technique.

Metallic Implants as Components of the Defect Stabilization/Reconstruction

It is imperative that all implants to be used for defect reconstruction/stabilization are made of titanium. Depending on the segmental defect location the following orthopaedic implants will be used for the Masquelet or the CTMC reconstruction surgery:

- *Intramedullary Nail for Defect Stabilization:* All eligible IM nails should have the option for static interlocking. No preference will be given to any specific nail type or manufacturer providing that the IM nail is cleared by the FDA for clinical use. The IM nail application will be in accordance with its approved indications and the manufacturer's recommended technique. These IM nails are part of a standard orthopedic surgery implant armamentarium.
  A) Humerus: Antegrade titanium statically-locked IM nail
  B) Tibia: Antegrade titanium statically-locked IM nail
  C) Femur: Antegrade titanium femoral statically-locked IM nail Cephalomedullary titanium statically-locked IM nail
  Retrograde titanium femoral statically-locked IM nail
- *Plate-Screw Construct for Defect Stabilization:* Locking plate and screw should be used as a mode of defect stabilization for cases in which an IM nail is not suitable. The plate should be of adequate size (length, thickness, width) to span across the defect and permit screw fixation which engages at least six cortices on each side of the defects. If applied in combination with the CTMC technique, the plate should be positioned at least 5 mm away from the external boundaries of the cortex to permit placement of the cage overlapping the defect ends.
- *Cylindrical Titanium Mesh Cage for Defect Reconstruction:* Presently there are two manufacturers of CTMCs available as surgical implants, and both CTMCs are cleared by the FDA for any osseous

reconstruction and/or reinforcement. The study will not designate the preferred cage; it will be left to the PIs' discretion. There are two cage types amenable for the CTMC technique:

A) Surgical Titanium Mesh™ (Harm's Cage; DePuy Motech, J&J, Warsaw, IN)

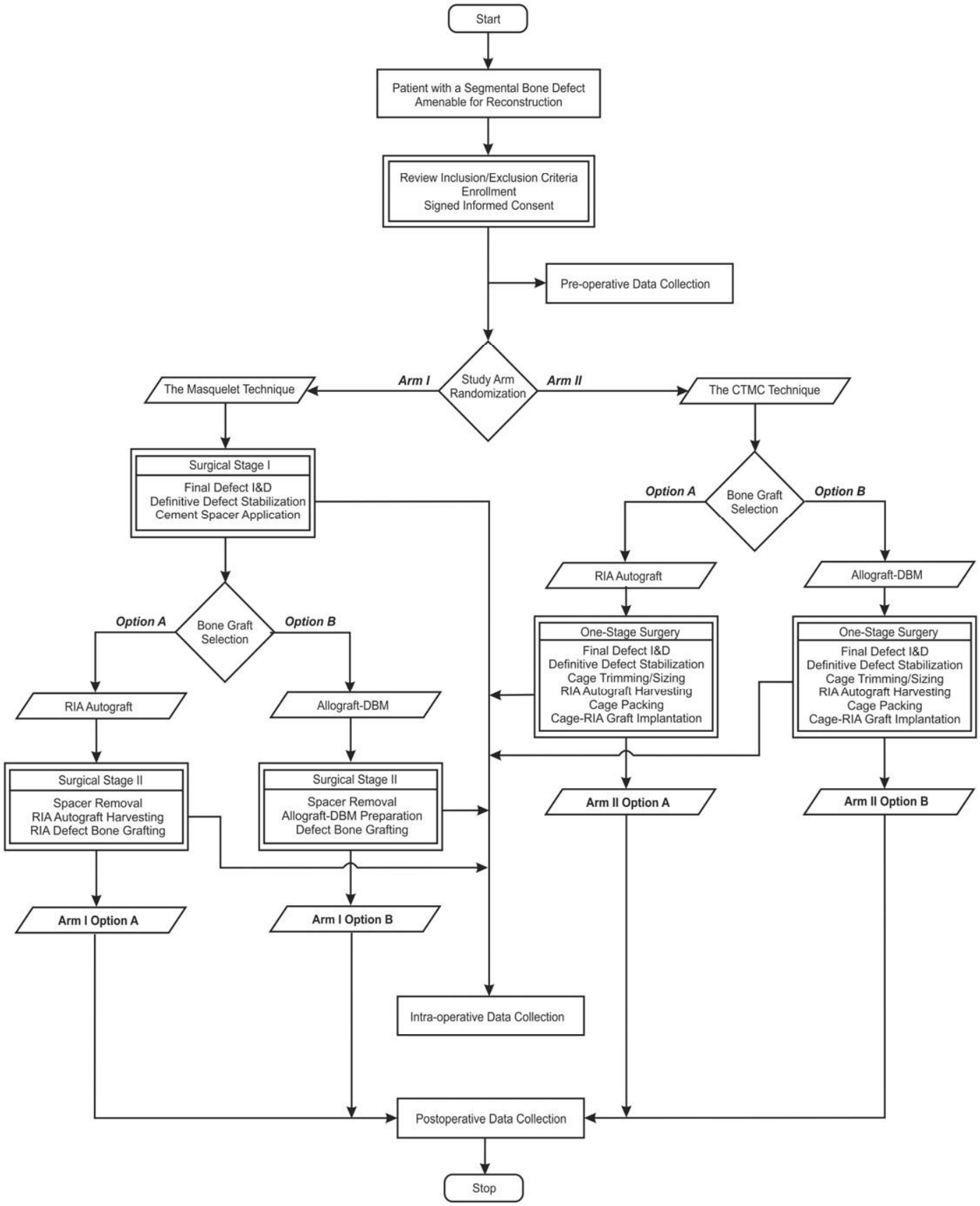
B) Pyramesh Titanium Mesh™ (Sofamor Danek-Medtronic, Memphis, TN)

Allograft Component (Option B) for the Defect Reconstruction

The following allograft bone graft from a tissue bank will be used in the study:

- Commercially-available, freeze-dried cancellous bone croutons approved for clinical application will be used. The Allograft (tissue) tracking number will be recorded. No preference will be given to the allograft provider on condition that it is in compliance with regulations and guidelines established by the FDA and the American Association of Tissue Banks. The intraoperative allograft handling and its application will strictly follow the provider's recommendations. The volume of the cancellous croutons should be sufficient to pack the cage.
- Demineralized bone matrix (DBM; Grafton Putty™; Osteotech®, Eatontown, NJ, USA) is allogeneic bone extract without bone mineral component. DBM demonstrates inherent osteoinductive properties, ie it induces *de novo* bone formation. DBM putty will be used in the study consistently. To eliminate inherent differences in osteoinductive properties that may occur between DBMs supplied by various vendors, in the trial consistently DBM putty supplied by Osteotech will be used Grafton Putty™ has gained FDA clearance/exempt for clinical use and it will be applied in full compliance and following the guidelines of the American Association of Tissue Banks. Grafton putty has well documented osteoinductive properties and it is the only DBM currently available on the market with clinical efficacy assessed and validated in a prospective clinical trial (Lindsey 2006). DBM putty will be uniformly mixed with allograft croutons in a ratio of approximately 1-to-3. The cancellous croutons-DBM composite will be used as the graft Option B to pack either the space within the biomembrane in the Masquelet technique or the cage in the CTMC technique.

Study-Specific Procedure Algorithm


Start
Patient with a Segmental Bone Defect Amenable for Reconstruction
Review Inclusion/Exclusion Criteria
Enrollment
Signed Informed Consent
Pre-operative Data Collection
Study Arm Randomization
Arm I
Arm II
The Masquelet Technique
The CTMC Technique
Surgical Stage I
Final Defect I&D
Definitive Defect Stabilization
Cement Spacer Application
Option A
Bone Graft Selection
Option B
RIA Autograft
Allograft-DBM
One-Stage Surgery
Final Defect I&D
Definitive Defect Stabilization
Cage Trimming/Sizing
RIA Autograft Harvesting
Cage Packing
Cage-RIA Graft Implantation
Surgical Stage II
Spacer Removal
RIA Autograft Harvesting
RIA Defect Bone Grafting
Spacer Removal
Allograft-DBM Preparation
Defect Bone Grafting
Arm I Option A
Arm I Option B
Arm II Option A
Arm II Option B
Intra-operative Data Collection
Postoperative Data Collection
Stop

Pre-, Intra-, and Post-operative Data Collection

	Clinical Exam	Imaging	Pain Score	Functional Assessment	Outcome Measure	QALY	Adverse Event
Preoperative	✓	X-ray	✓	✓	✓	✓	
Intraoperative	✓						✓
Postoperative							
Immediate postop	✓	X-ray					✓
2 weeks	✓	X-ray	✓	✓			✓
6 weeks	✓	X-ray	✓	✓			✓
3 months	✓	X-ray	✓	✓	✓		✓
6 months	✓	X-ray	✓	✓	✓		✓
12 months	✓	X-ray CT	✓	✓	✓	✓	✓
18 months	✓	X-ray	✓	✓	✓	✓	✓

DATA MANAGEMENT:

Methods of Data Collection

A study specific Case Report Form (CRF) will be designed in accordance to the following principles:

- has unique coded subject study identifier (ID);
- is consistent with the study protocol;
- gathers study data accurately and reliably;
- organizes and labels forms and fields to permit intuitive data entry;
- has error- and/or omission-proof design;
- avoids redundancy;
- facilitates data entry into the study database.

All data collected in the study will be stored in both printed (hard) and electronic (soft) formats. Customized data collection forms (source documents) will be used to ensure the consistency and thoroughness or the data acquisition process. The PIs will periodically review the data for its completeness and accuracy. Subject identifiers

will be removed from study data collection forms, and the subject will be assigned a specific study ID code with a consecutive number. Critical measurements on data collection forms will be bolded.

Identifiers

The enrolled subjects will be given a study ID code according to the following coding system:

code: **TRIAL-XX-MM/YY**; where:

XX – the consecutive study subject number
MM/YY – date of the enrollment (month/year)

A list (key) of these codes assigned to the specific subjects' names will be kept secure by the PIs.

Confidentiality

Study records and all information that can identify the subject will be kept confidential as per the federal privacy regulations provided under the Health Insurance Portability and Accountability Act (HIPAA) to protect the privacy, security, and authorized access of patient records. Following HIPAA regulations subject authorization is obtained in the signed informed consent for the use and disclosure of subject's health information but only for the purpose of completing this clinical study. Except when required by law, the subject will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of study center (UTMB). For all records and information disclosed outside of the UTMB, the subject will be assigned a specific study ID code number. The key to the code will be kept in a locked file in PI's (Z.G.) office.

UTMB institutional policy and guidelines mandate that all study PIs and all members of the research team successfully complete HIPAA and CITI Basic Course and Health Information Privacy & Security (HIPS) Training for Clinical Investigators.

All data collected in the study will be stored in a secured location. Data in an electronic format will be stored in a PC and backed up daily. The backup tape will be kept in a fireproof safe with a biometric lock. The access to the computer with the stored study data will be password controlled (128-bit encryption algorithm). Hard copies of the study data will be stored in binders dedicated for each study subject; these will be kept in a locked clinical research office with limited access of only approve study personnel.

The study data will be kept for a minimum of 10 years after the study completion/termination in accordance with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and in accordance with all local laws (UTMB) for retention of study records.

SCREENING PROCEDURES:

All medical and surgical care will be conducted in accordance with accepted healthcare standards. If the subject is female of child-bearing age, and has not undergone a sterilization procedure, a serum pregnancy test will be required in order to rule out pregnancy. Female subjects with child-bearing potential will be advised to refrain from becoming pregnant while in the study. A urine and serum pregnancy test will be done at time of enrollment and again prior to surgery, respectively.

Patients presenting to the UTMB hospital will undergo standard general medical and orthopedic examinations and routine biplanar plain radiography as a screening for presence of segmental bone defect or a medical condition (infection, nonunion, tumor) treatable by iatrogenic segmental bone resection. Specific routine laboratory workup

(blood test, microbiology, biopsy, etc) will be performed to diagnose the patient's specific medical condition, and their eligibility for the iatrogenic segmental bone resection as a suitable treatment. Informed consent will be obtained prior to initiation of any screening procedures for the purpose of determining study eligibility.
All subjects will undergo routine preoperative laboratory testing for surgery screening (standard of care). These laboratory studies will include complete blood cell count with differential; basic metabolic profile; electrocardiogram for subjects greater than or equal to age 50. Additional standard of care studies may be ordered depending on the subject's underlying medical condition and specific anesthesiologist's clearance for surgery protocol will be required.

RISKS / BENEFITS ASSESSMENT:

Foreseeable Risks

Segmental bone defect represents a formidable treatment challenge. The complexity of this condition often results in many complications associated with all currently available treatment options. All these treatment modalities for segmental bone defects are considered high risk, and therefore, are frequently applied as limb salvage operations. Because of the high inherent risks and complications, all currently available segmental bone defect treatment procedures carry the ultimate risk of limb amputation.

The potential specific risks for the subject participating in the study may be related to:

- Cement Spacer: The potential side effects associated with using the cement space include pain excessive scarring, and dislodgment.
- Cage: The potential side effects associated with using the CTMC for bone defect reconstruction include local infection, inflammation, cage dislodgment (change of its initial position), and pain.
- Bone Graft: The potential side effects associated with using bone graft or bone graft substitute are the same as in all existing surgical procedures associated with bone grafting and may include:
  A) RIA-harvested autograft (Option A): harvesting site infection, pain, and fracture;
  B) allograft-DBM (Option B): local infection and/or inflammation about the defect, delayed or minimal healing of the defect;
- Radiation from imaging studies: The amount of radiation to which the subject will be exposed throughout the study to monitor the defect healing is relatively small and not different from the standard follow-up radiation for all other techniques currently applied for bone defect reconstruction. This amount of radiation may be potentially harmful, but these risks are so small that they are difficult to measure.
- Confidentiality: Participation in the research study is confidential although it may involve some loss of privacy. Subject study research records will be handled as confidentially as possible within the law, and the researchers will follow all federal and institutional regulations. In order to verify the study data, independent research individuals from the sponsoring agency (the Department of Defense) or the FDA may access study records. No information that could specifically identify the subject will be used in any reports or publications resulting from this study.

Risk Management and Emergency Response

Routine measures (standard of care) will be taken to minimize and/or eliminate risks to the study subjects. These risks will be monitored and mitigated in accordance to the subject's medical condition and the pre- and post-reconstruction medical interventions. Subjects will be routinely followed in the post defect reconstruction and beyond the study designated time points, if necessary (in case of ongoing adverse events or pregnancy).

As per a study inclusion criterion, eligible female patients must have a negative serum pregnancy test to be enrolled into the study. Female subjects enrolled in the study will be encouraged not to get pregnant throughout the entire study period (ie, 18 months). If subject pregnancy occurs, it will be documented. The subject will be advised to notify her obstetrical physician. If the resulting birth is abnormal, the abnormality will be reported as an adverse event.

If the subject sustains physical injury or contracts a disease because of any substance given or procedure performed due to participation in this study their injury will be treated. The subject's medical insurance will be billed and any charges not covered by the subject's insurance or health care program will be the subject's responsibility. In addition, the subject will be responsible for paying any costs related to illnesses and medical events that are not associated with participating in the study.

ADVERSE EVENTS:

The PIs and the members of the study research team are responsible for the detection and documentation of events defined as an adverse event (AE). The investigators are also responsible for appropriate documenting and reporting of all AEs.

AE monitoring will be conducted at all follow-up intervals (including also those intervals not mandated by the protocol).

AE is defined as any adverse event, whether or not that event is felt to be related, occurring at the time of study. AEs will be treated in accordance with accepted medical standards and documented in the subject's study record and monitored by the PIs and research team. AEs will be reported to the UTMB IRB and to the US Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office (HRPO).

All AEs will be assessed to determine the following:

A) whether event meets the criteria for an AE;
B) the relationship to study treatment;
C) the severity of the event;
D) the "expectedness" of the event.

All recorded AEs will include the following information:

A) specific condition or event;
B) dates and times of occurrence;
C) severity;
D) treatment and outcome.

<u>AE Rating</u>

AEs will be rated for severity/intensity according to the following criteria:

- <u>Mild:</u> easily tolerated, causing minimal discomfort and not interfering with normal everyday activities;

- Moderate: sufficiently discomforting to interfere with normal everyday activities (the subject is able to continue in the study; treatment for symptoms may be needed);
- Severe: incapacitating and/or preventing normal everyday activities (severity may cause cessation of the study, treatment for symptoms is needed).
- Life-Threatening or Disabling
- Lethal

AE Relation to the Study Treatment

The following definitions will be considered in assessing the relationship of AEs to the study treatment:

- Not related: the event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject;
- Unlikely: any event that does not follow a reasonable temporal sequence from administration of study treatment *or* that is likely produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject;
- Possible: the event follows a reasonable temporal sequence from administration of study treatment *or* that follows a known response pattern to the study treatment, but could have been produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject;
- Probable: the event follows a reasonable temporal sequence from administration of study treatment; and cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject;
- Related: the event follows a reasonable temporal sequence from the time of study treatment; and cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject.

AE and Pre-existing Conditions

The occurrence of a sign or symptom of a pre-existing condition during the study is not an AE, unless the condition worsened in either intensity or frequency. Pre-existing conditions are those illnesses, abnormalities, or problems that were part of the patient's medical history prior to the baseline visit and all of these conditions will be recorded.

AE Reporting

All unanticipated problems involving risk to study subjects or others, AEs related to participation in the study, and all subject deaths related to participation in the study will be promptly reported by phone, email, or by fax to the UTMB IRB and the US Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office. A complete written report will follow the initial notification.

Potential Study Benefits

There is no direct benefit to the subject for participation in this study.

Society Study Benefits

It is hoped that the information gained from the study will help in the treatment of future patients with segmental bone defects.

IRB GUIDELINES - DATA AND SAFETY MONITORING PLAN TEMPLATE

Federal regulations require the IRB to determine that research plans submitted provide adequate provisions for monitoring data collected in order to ensure the safety of subjects. Monitoring should be commensurate with risks and with the size and complexity of the trials. Phase III clinical trials generally require a data and safety monitoring board. Investigators involved in Phase I and II clinical trials must submit a general description of the data and safety monitoring plan as part of the research application and as part of the protocol submission to the IRB. The following template is provided for UMASS investigators as a guide to developing a data and safety monitoring plan.

I. Protocol Title: The Comparative Efficacy of the Masquelet versus Titanium Mesh Cage Reconstruction Techniques for the Treatment of Large Long Bone Deficiencies

II. Oversight of this Investigation will be provided by the study PI: Zbigniew Gugala, MD,PhD; Department of Orthopaedic Surgery; University of Texas Medical Branch, Galveston, TX; Phone: 409-747-5760; Fax: 409-747-5747; Email: zgugala@utmb.edu; and **the study co-PI:** Ronald W. Lindsey, MD; Department of Orthopaedic Surgery; University of Texas Medical Branch, Galveston, TX; Phone: 409-747-5700; Fax: 409-747-5747; Email: rlindsey@utmb.edu

III. Purpose of the Study:

Background: Segmental long bone defects remain a formidable treatment challenge. All the existing standard treatment options have major limitations and often culminate in limb amputation or permanent functional deficits. We developed a novel, one-stage alternative treatment for segmental bone loss that utilizes the cylindrical titanium mesh cage (CTMC) in combination with bone graft, and have established its clinical merits in an initial clinical series. Shortly thereafter, Masquelet reported another new defect reconstruction technique that involves two-stage approach: first inducing biomembrane formation with a cement spacer, and subsequent spacer removal and bone grafting. Both the Masquelet and the CTMC techniques are based on the principle of graft containment to render optimal potential for graft to heal the defect; however, they differ in primary biological versus biomechanical functions provided by the containment. The Masquelet biomembrane containment, being a rich source of vascular supply and growth factors, creates an excellent biological milieu for graft, but requires an additional surgery and is associated with prolonged protected weight bearing until graft consolidation occurs. Conversely, the benefit of the CTMC technique is primarily the biomechanical support it provides for graft and the reconstructed extremity, thereby permitting immediate functional restoration without mobility or weight bearing restrictions during the bone healing process. Although both Masquelet and the CTMC techniques have been effective in the treatment of large segmental bone defects, there is no prospective, well-controlled study comparing their therapeutic efficacies for specific clinical indications.

Overall objective: Determining the clinical efficacy and cost-effectiveness of the Masquelet (Arm I) versus the CTMC technique (Arm II) in combination with RIA-harvested autograft (Option A) or allograft-demineralized bone matrix composite (Option B) in the treatment of segmental long bone deficiencies.

Specific Aims: 1) Establish the effects of the specific patient and bone defect characteristics on the treatment outcome; 2) Determine and compare clinical efficacies of the reconstruction techniques (Arm I vs Arm II); 3) Establish the merits of using specific graft type (Option A vs Option B) within and across each study arms; 3) Develop a quantitative predictive model to improve clinical decision making, and 4) Assess and compare the cost-effectiveness and resource expenditures incurred by the specific treatment selection.

Study Design: Single-center, 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. The data collected will include routine patient baseline information, systemic and extremity injury characteristics, bone defect characteristics, pre- and post-operative clinical examinations and imaging, validated functional outcomes measures, and associated cost expenditure. Descriptive statistics will be used to analyze and compare the results specifically related to the rate of defect healing and functional recovery. Paired t-test will be used to test the effects of the defect reconstruction option on the outcome measures. Analysis of covariance will be used for pair-wise comparison between the arms and within/across each bone graft option. Multiple models will be used to produce an accurate predictive model which accounts for possible morbidities and interactions. Derived from the joint distribution of costs and effects, cost-effectiveness acceptability curves will be established and compared for the study arms.

Civilian/Military Relevance: Many combat injuries involve extremity trauma with segmental bone loss, and the extent to which they can be successfully treated impacts the function and quality of life of the wounded warrior. The Masquelet and the CTMC have been developed for civilians in the civilian clinical setting as innovative, biologically-sound defect reconstructive techniques to address the complexity of therapeutic concerns associated with these conditions (ie, immediate restoration of limb alignment/stability, early motion, weight bearing). The proposed trial aims to compare the efficacy of these techniques to identify the one that can be instantly adopted and applied by military surgeons.

IV. Assessment of Level of Risk

There is minimal risk associated with the participation in the study. Both treatment options (clinical trial arms), the Masquelet and the CTMC technique are approved by the FDA are considered as the standard of care for the treatment of segmental bone loss. The research component of the study incudes the randomization to one of the two the study arm, collecting the routine medical record and medical chart data, and completing subjective outcome questionnaires. The PI and co-PI will monitor for potential adverse events (AEs) that may occur in the study and will notify the UTMB IRB immediately if these occur. The questionnaires applicable in the trails will pertain solely to subject's subjective outcome and will not pose harm or discomfort for study subjects.

Routine measures (standard of care) will be taken to minimize and/or eliminate risks to the study subjects. These risks will be monitored and mitigated in accordance to the subject's medical condition and the pre- and post-reconstruction medical interventions. Subjects will be routinely followed in the post defect reconstruction and beyond the study designated time points, if necessary (in case of ongoing adverse events or pregnancy).

As per a study inclusion criterion, eligible female patients must have a negative urine pregnancy test to be enrolled into the study, and serum pregnancy test prior to the surgery (standard of care). Female subjects enrolled in the study will be encouraged not to get pregnant throughout the entire study period (ie, 18 months). If subject pregnancy occurs, it will be documented. The subject will be advised to notify her obstetrical physician. If the resulting birth is abnormal, the abnormality will be reported as an adverse event.

If the subject sustains physical injury or contracts a disease because of any substance given or procedure performed due to participation in this study their injury will be treated. The subject's medical insurance will be billed and any charges not covered by the subject's insurance or health care program will be the subject's responsibility. In addition, the subject will be responsible for paying any costs related to illnesses and medical events that are not associated with participating in the study.

V. Plan for Monitoring Safety/Confidentiality

The PI and co-PI (as listed above) will be responsible for monitoring the safety environment of the participants.

Conditions that would necessitate termination of the subject participation in the study after the subject has been enrolled and/or reach study end point include:

- intraoperative determination of need for surgical procedure outside the study scope or protocol;
- identifying any valid exclusion criterion after the subject's enrollment;
- secondary procedure disrupting or preventing implementation of either the Masquelet or the CTMC defect reconstruction technique as in the study protocol;
- evidence of infection or neoplasm recurrence post defect reconstruction;
- evidence of vascular compromise in the affected extremity resulting in secondary intervention affecting healing; • subject declines continued participation;
- subject is non-compliant with follow up care and instructions;
- termination for any reason deemed mandatory by the PIs;
- defect is completely healed before the end of the follow-up (ie, 24 months); • subject becomes pregnant before the defect reconstructive surgery;
- subject completes the study.

The PIs will be study medical monitor and they will ensure that:

- only subjects who meet the study eligibility criteria are enrolled.
- the informed consent process will be conducted appropriately and that informed consent will be obtained prior to proceeding with any study procedures. (any problems with the obtaining the informed consent .
- data will be collected and analyzed strictly as designated in the protocol.
- adverse events (AEs) will be reviewed promptly and reported as required (see Section VII below).

Study records and all information that can identify the subject will be kept confidential as per the federal privacy regulations provided under the Health Insurance Portability and Accountability Act (HIPAA) to protect the privacy, security, and authorized access of patient records. Following HIPAA regulations subject authorization is obtained in the signed informed consent for the use and disclosure of subject's health information but only for the purpose of completing this clinical study. Except when required by law, the subject will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of study center (UTMB). For all records and information disclosed outside of the UTMB, the subject will be assigned a specific study ID code number. The key to the code will be kept in a locked file in PI's (Z.G.) office.

VI. Plan for Data Management

PI (Z.G.) and the study coordinator will responsible for collection and storage of data.

A study specific Case Report Form (CRF) will be designed in accordance to the following principles:

- has unique coded subject study identifier (ID);
- is consistent with the study protocol;
- gathers study data accurately and reliably;
- organizes and labels forms and fields to permit intuitive data entry;
- has error- and/or omission-proof design;

- avoids redundancy;
- facilitates data entry into the study database.

All data collected in the study will be stored in both printed (hard) and electronic (soft) formats. Customized data collection forms (source documents) will be used to ensure the consistency and thoroughness or the data acquisition process. The PIs will periodically review the data for its completeness and accuracy. Subject identifiers will be removed from study data collection forms, and the subject will be assigned a specific study ID code with a consecutive number. Critical measurements on data collection forms will be bolded.

Identifiers: The enrolled subjects will be given a study ID code according to the following coding system: code: TRIAL-XX-MM/YY; where:

XX – the consecutive study subject number

MM/YY – date of the enrollment (month/year)

A list (key) of these codes assigned to the specific subjects' names will be kept secure by the PIs.

All data collected in the study will be stored in a secured location. Data in an electronic format will be stored in a PC and backed up daily. The backup tape will be kept in a fireproof safe with a biometric lock. The access to the computer with the stored study data will be password controlled (128-bit encryption algorithm). Hard copies of the study data will be stored in binders dedicated for each study subject; these will be kept in a locked clinical research office with limited access of only approve study personnel.

The study data will be kept for a minimum of 10 years after the study completion/termination in accordance with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and in accordance with UTMB laws for retention of study records.

VII. Adverse Event (AE)

The PIs and the members of the study research team are responsible for the detection and documentation of events defined as an adverse event (AE). The investigators are also responsible for appropriate documenting and reporting of all AEs.

AE monitoring will be conducted at all follow-up intervals (including also those intervals not mandated by the protocol).

AE is defined as any adverse event, whether or not that event is felt to be study related, occurring at the time of study. AEs will be treated in accordance with accepted medical standards and documented in the subject's study record. AEs will be reported to the UTMB IRB and to the US Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office (HRPO).

All AEs will be assessed to determine the following:

- whether event meets the criteria for an AE;
- the relationship to study treatment;
- the severity of the event;
- the "expectedness" of the event.

All recorded AEs will include the following information:

- specific condition or event;
- dates and times of occurrence;
- severity;
- treatment and outcome.

AE Rating: AEs will be rated for severity/intensity according to the following criteria:

- Mild: easily tolerated, causing minimal discomfort and not interfering with normal everyday activities;

- Moderate: sufficiently discomforting to interfere with normal everyday activities (the subject is able to continue in the study; treatment for symptoms may be needed);
- Severe: incapacitating and/or preventing normal everyday activities (severity may cause cessation of the study, treatment for symptoms is needed).
- Life-Threatening or disabling.
- Lethal

AE Relation to the Study Treatment: The following definitions will be considered in assessing the relationship of AEs to the study treatment:

- Not related: the event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject;
- Unlikely: any event that does not follow a reasonable temporal sequence from administration of study treatment *or* that is likely produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject;
- Possible: the event follows a reasonable temporal sequence from administration of study treatment *or* that follows a known response pattern to the study treatment, but could have been produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject;
- Probable: the event follows a reasonable temporal sequence from administration of study treatment; and cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject;
- Related: the event follows a reasonable temporal sequence from the time of study treatment; and cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant medications administered to the subject.

AE and Pre-existing Conditions: The occurrence of a sign or symptom of a pre-existing condition during the study is not an AE, unless the condition worsened in either intensity or frequency. Pre-existing conditions are those illnesses, abnormalities, or problems that were part of the patient's medical history prior to the baseline visit and all of these conditions will be recorded.

AE Reporting: All unanticipated problems involving risk to study subjects or others, SAEs related to participation in the study, and all subject deaths related to participation in the study will be promptly reported to the UTMB IRB by phone, email, or by fax. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the US Army Medical Research and Materiel Command, ATTN: MCMRZB-P, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

VIII. Protection of Human Research Participants-Computer Based Training

As per the UTMB institutional policy and guidelines, the study PIs and all members of the research team will successfully complete HIPAA and CITI Basic Course and Health Information Privacy & Security (HIPS) Training for Clinical Investigators.

The University of Massachusetts Amherst Institutional Review Board will approve this plan, with the project protocol, prior to implementation of the study.

STUDY TIME FRAME:

With a proposed study duration of 4 years, the timeline for allocating research efforts and expected objective accomplishments is as follows:

1. Preparatory period (0-6 months)

This period encompasses the time from grant notification to study initiation (approximately 6 months). During this period the following task wills be accomplished:

- Obtain UTMB Institutional Review Board (IRB) approval for the study (timeframe 1-3 months);
- Finalize all necessary research agreements with the study's participating hospital sites;
- Construction of study specific Case Report Form (CRF);
- Design of study database to capture and process all collected study variables; *Milestone #1: IRB approval*

2. Study Enrollment Period (32 months)

This period encompasses the timeframe of the first 32 months from study initiation. This period's primary objective is to successfully enroll 30 eligible patients in the study. In case of slow accrual, specific measures (enhanced referral program, study advertisement, etc) will be taken. During this period the following study tasks are expected to be accomplished:

- Continuing enrollment of the eligible patients as study subjects;
- Preoperative (baseline) subject data collection;
- Preoperative patient management;
- Perform the Masquelet or the CTMC defect reconstruction surgery;
- Intraoperative data collection;
- Immediate and early postoperative data collection

Milestone #2: Enrollment of 30 eligible patients
Milestone #3: The Masquelet or CTMC defect reconstructive surgery

The recorded preoperative study variables will permit realization of the following study objectives:

- Determine the perioperative safety and efficacy of the Masquelet versus the CTMC defect reconstructive technique;
- Identify the specific indications for performing the Masquelet versus the CTMC technique among the enrolled subjects;
- Provide a thorough characterization of the patient population that presents with segmental bone defects that warrant surgical reconstruction (specific aim 1);
- Establish defect characteristics among the study subjects treated with the Masquelet versus the CTMC procedure (part of specific aim 2);
- Collect and analyze the distribution of patients within specific study arms (Option A vs Option B) (part of specific aim 3);
- Establish the cost or preoperative and surgical management of the study subjects;
- Provide an analysis of patients with segmental bone deficiency who did not meet study eligibility criteria;
  - Establish the extent of patient compliance with immediate and early postoperative regimen.

3. Study Follow-up Period (18 months)

This period encompasses the timeframe of the last 18 months, i.e. from termination of enrollment to study completion. This period's primary objective is to successfully complete follow-up of all enrolled patients. During this period the following study tasks are expected to be accomplished:

- Continuing postoperative data collection;
- Analysis of data collection process (consistency, redundancy, dropout rate);
- Tentative statistical analysis of the collected data;
- Establish costs of subject follow-up incurred;
- Itemize all resource expenditure for total treatment costs assessment.

Milestone #4: Follow-up completion of 30 study subjects

4. Study Post Completion Period (2-4 months)

This period encompasses the timeframe after the study has been terminated. The research efforts in this period include:

- Thorough analysis of all pre-, intra-, and postoperative variables collected in the study to accomplish the specific study aims 2, 3 and 4.
- Assessment of the safety and efficacy of the CTMC defect reconstructive technique
- Establishing the clinical indications and treatment recommendation for CTMC the based upon the treatment outcome;
- Assessment of the total resource expenditure related to the CTMC reconstruction technique (in accordance with the graft option type) and comparison with the standard defect reconstruction modalities (study specific aim 5);
- Data presentation at international/national research meetings.
- Manuscript preparation and submission to a high-impact-factor peer-reviewed journal.

Milestone #5: Data presentation in research forums
Milestone #6: Manuscript publication