

A Prospective, Multi-Center Study of the IlluminOss[®]
Photodynamic Bone Stabilization System for the
Treatment of Impending and Actual Pathological
Fractures in the Humerus from Metastatic Bone Disease

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Study Protocol

January 6, 2016

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Protocol Number: 14-03-PATHOLHUM-02

**Sponsor: IlluminOss Medical, Inc.
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Prior to participation in this study, the appointed Principal Investigator at the Investigational Site (hereafter referred to as “Principal Investigator” or “PI”) must obtain written approval from his/her Institutional Review Board (IRB). This approval must be in the PI’s name and a copy of the approval letter must be sent to the Sponsor, IlluminOss Medical, Inc. or their representative along with the IRB approved Informed Consent Form and the signed Clinical Study Agreement (CSA), prior to the first clinical use of the investigational device.

The PI must also:

- Conduct the study in accordance with the 21 CFR Part 812, 21 CFR Part 50, the study protocol, the signed CSA, Good Clinical Practices, the Declaration of Helsinki, and all applicable national/local regulations.
- Agree to participate in an appropriate training program prior to study initiation.
- Assure that informed consent is obtained from each patient prior to enrollment, using the IRB-approved form.
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- Complete all case report forms (CRFs) and study documentation and relevant imaging assessments (as required) and submit promptly to the Sponsor, IlluminOss Medical, Inc. and/or its authorized representative for data management.

The PI may delegate one or more of the above functions to an associate or Co-Investigator. However, the PI retains overall responsibility for proper conduct of the study, including obtaining and documenting subject informed consent, compliance with the study protocol, and the collection of all required data.

Investigator Signature

I have read and understand the contents of this protocol. I agree to follow and abide by the guidelines set forth in this document.

Principal Investigator Name (print)

Principal Investigator Signature

Date

Abbreviation	Meaning
ADE	Adverse Device Effects
ADL	Activities of Daily Living
AE	Adverse Event
AO	Arbeitsgemeinschaft für Osteosynthesefragen (Association for the Study of Internal Fixation)
AP	Anterior/posterior
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSA	Clinical Study Agreement
EU	European Union
FDA	Food and Drug Administration
ICF	Informed Consent Form
IFU	Instructions for Use (device)
IM	Intramedullary
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MBD	Metastatic Bone Disease
MSTS	Musculoskeletal Tumor Society
OPC	Objective Performance Criteria
PBSS	IlluminOss Photodynamic Bone Stabilization System

PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIIC	Subject Information & Informed Consent form
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAEs	Treatment-Emergent Adverse Events
VAS	Visual Analog Scale

Revision History

Version and Date	Changes
Version 1.0: 26 August 2014	Not applicable
Version 2.0: 20 November 2014	<ul style="list-style-type: none"> • Revised entry criteria to allow for other metastatic bone lesions not affecting the target humerus, clarifies that the minimum Mirel's score is subject to minimum VAS score requirements • Increased date range for Day 7 visit to 14 days (+3 days) to reflect standard of care visit scheduling • Amended Adverse Event terminology to align with CFR.
Version 3.0: 14 January 2015	<ul style="list-style-type: none"> • Revised entry criteria to further clarify exclusion of patients with functional deficit of humerus or focal neurologic deficit • Added CMS required language for Medicare beneficiary coverage
Version 4.0: 24 September 2015	<ul style="list-style-type: none"> • Revised entry criteria to require a minimum 60mm VAS score at Baseline • Updated Statistical methods section to provide for an interim analysis
Version 5.0: 6 January 2016	<ul style="list-style-type: none"> • Clarified analysis of primary endpoint • Clarification of radiographic views

Protocol Synopsis

Title:	A Prospective, Multi-Center Study of the IlluminOss® Photodynamic Bone Stabilization System for the Treatment of Impending and Actual Pathological Fractures in the Humerus from Metastatic Bone Disease
Device:	IlluminOss Photodynamic Bone Stabilization System (PBSS)
Study Objective:	The primary objective of the study is to evaluate safety and performance data of the PBSS when used for the treatment of painful impending and actual fractures of the humerus secondary to metastatic malignancy. Results from this study will be used to confirm clinically and statistically significant reductions in pain and improvements in function among patients presenting with painful impending or actual fractures.
Study Design:	US FDA marketing clearance, prospective, multi-center, open label study.
Sample Size:	An enrollment of 80 subjects is planned for this clinical study
Study Duration	Enrollment is expected to take approximately 12 months. Study subjects will be followed through the Day 90 Visit, followed by the extended follow up phase out to the Day 360 Visit.
Subject Population:	The investigation population consists of skeletally mature adults, suffering from pain due to impending and actual pathological fractures of the humerus secondary to metastatic malignancy.

<p>Inclusion Criteria:</p>	<p><u>General Inclusion Criteria</u></p> <ol style="list-style-type: none"> 1. Skeletally mature adult males and females 18 years of age or older. 2. Impending or actual pathological fracture of the humerus, secondary to metastatic bone disease. 3. Females: neither pregnant nor intending to become pregnant during the course of the study, defined as: <ol style="list-style-type: none"> a. Postmenopausal for at least 1 year OR b. Documented oophorectomy or hysterectomy c. Surgically sterile OR d. If of childbearing potential, must be practicing double-barrier method of birth control, be willing to avoid pregnancy for the period of study participation and have a negative pregnancy test at screening 4. Patient, or his/her legally authorized representative, is able to understand and provide informed consent. 5. Willing and able to comply with post-operative treatment protocol and follow-up visit schedule. 6. VAS Pain Score \geq 60mm on 100mm scale <p><u>Impending Fracture-Specific Inclusion Criteria</u></p> <ol style="list-style-type: none"> 7. Documented presence of at least one metastatic lesion of the humerus. 8. Mirels Criteria Score \geq 8. (specific to the target humeral lesion and subject to minimum VAS score requirements) 9. Destruction of cortical bone at impending fracture site $>$ 50%. <p><u>Actual Fracture-Specific Inclusion Criteria</u></p> <ol style="list-style-type: none"> 10. Fracture is closed, Gustilo Type I or II.
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Exclusion Criteria:	<p><u><i>General Exclusion Criteria</i></u></p> <ol style="list-style-type: none">1. Primary tumor (osteogenic origin, etc.) at site.2. Impending or actual fracture at any other location, that, in the Investigator's opinion, would preclude ability to assess pain and/or function in the target humerus3. Active or incompletely treated infections that could involve the device implant site.4. Distant foci of infection that may spread to the implant site.5. Allergy to implant materials or dental glue.6. In the investigator's judgment, functional deficit in the target humerus with an etiology other than bone metastases (e.g. due to vascular insufficiency).7. In the investigator's judgment, focal neurologic deficit as a result of metastases in the brain, spine, or other central nervous system disorders.8. Uncooperative patients, or patients who are incapable of following directions (for example, as a consequence of a neurological or psychiatric disorder).9. Prisoner. <p><u><i>Impending Fracture-Specific Exclusion Criteria</i></u></p> <ol style="list-style-type: none">10. Mirels Score < 8 (specific to target humeral lesion).11. Destruction of cortical bone at impending fracture site < 50%.12. Prior surgery and/or prior fracture of affected site.13. Any articular component to impending fracture site. <p><u><i>Actual Fracture-Specific Exclusion Criteria</i></u></p> <ol style="list-style-type: none">14. Open fractures with severe contamination.15. Extremely comminuted fractures where insufficient holding power of the balloon on the intramedullary canal is probable.16. Patients whose intramedullary canal at site of fracture measures smaller than the diameter of the sheath provided.
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<p>Primary Endpoint:</p>	<p>Pain Reduction</p> <ul style="list-style-type: none"> • Change in VAS Pain Score at Day 90 <p>Functional Improvement</p> <ul style="list-style-type: none"> • Change in Revised Musculoskeletal Tumor Society Rating Scale for Upper Extremity (MSTS) at Day 90 <p>Primary effectiveness will be evaluated relative to literature-based historical controls. These were selected on the basis of comparability to the target population and similarity to the investigational device. There are two primary effectiveness endpoints, reduction in pain at 90 days relative to pre-treatment baseline and improvement in function at 90 days relative to pre-treatment baseline. The changes in VAS pain and MSTS from pre-treatment baseline to day 90 will be involved in the primary effectiveness tests to be applied to enrolled patients who have actual or impending fractures, with VAS pain scores of at least 60mm. Non-inferiority of mean changes at Day 90 will be compared relative to reference values determined through evaluation of historical controls. Testing for pain reduction will first be performed. Only if the null hypothesis of inferiority in mean VAS pain improvement at Day 90 is rejected at $p < 0.05$, will the co-primary endpoint MSTS be similarly tested.</p> <p><u>Safety Success</u> is evaluated according to a composite endpoint by meeting all of the following criteria:</p> <ul style="list-style-type: none"> • Clinical <ul style="list-style-type: none"> ○ No Serious Device Related Complications ○ No additional surgical interventions: <ul style="list-style-type: none"> ▪ Revisions, supplements, fixations, or removals • Radiographic <ul style="list-style-type: none"> ○ No device fracture, migrations, mal-alignment or loss of reduction or fixation <p>The number and percentage of patients achieving the Safety Success endpoint will be reported cumulatively for days 7-14, 30, and 90 and 180 and 360 and with 95% 2-sided exact binomial confidence intervals.</p>
<p>Secondary Endpoints</p>	<p>The secondary endpoints, evaluated at the Day 90 Visits, include:</p> <ul style="list-style-type: none"> • The individual components of the safety endpoint • Other secondary endpoints include: <ul style="list-style-type: none"> ○ Duration of index procedure and length of hospital stay ○ Activities of Daily Living score through all follow-up intervals ○ Disability status

	<ul style="list-style-type: none"> ○ Evaluation of duration of physical therapy prescription ○ Assessment of prescription and over-the-counter analgesic medication use ○ Survivability from time of index procedure to death <p>The safety endpoints evaluated through Day 90, also include:</p> <ol style="list-style-type: none"> 1. Incidence and number of AEs. 2. Incidence and number of procedure and device-related complications. <p>These secondary endpoints listed above will also be examined during the extended follow up portion of the trial at Day 180 and 360.</p>
Interim Analysis	After 30 patients have been treated and followed for 90 days, an interim analysis on change from baseline VAS to 90 days will be carried out. The purpose of this interim analysis is to asses for: (a) potentially stopping the trial for futility; and (b) potentially increase the sample size if the improvement in the VAS at 90 days is large, but not as large as anticipated in the original sample size calculations.
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Regulatory Responsibility	IlluminOss Medical, Inc. 993 Waterman Avenue East Providence, RI 02914 USA Tel: 401-714-0008 Fax: 401-714-0009
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1 Introduction

1.1 Impending Pathological Fractures from Cancer

Background

Metastases from cancer are the most common malignancy involving the skeletal system.¹ In the United States alone, of the over 1.4M (2011) patients diagnosed with cancer annually, over 700,000 will be diagnosed with metastases to bone in addition to an underlying prevalence of 280,000 cases.^{1, 2} Compared to the relatively few primary bone cancers per year, with an incidence of 3,010 (2013)³, the economic burden of metastatic disease to bone is enormous: consuming \$12.6B (2007) in healthcare spend and 17% of the \$74B in total direct cost of oncologic care estimated by the National Institutes of Health.⁴ Prevalence, incidence, and cost estimates for metastatic bone disease (MBD) are projected to continue growing as with improved medical treatment of many primary cancers, patients are living longer, becoming more likely to develop distant bone metastases.⁵

The skeleton is the third most common target of distant metastases⁴, following lung and liver. The axial skeleton is predominantly affected, with MBD of the spine occurring 40 times more frequently than all primary bone tumors combined.⁶ After the axial skeleton, MBD affects the femur, humerus, and tibia in decreasing incidence. Studies at post-mortem have revealed MBD following carcinomas of the breast in 73% of patients, prostate (63%), thyroid (42%), kidney (35%), and lung (36%); gastrointestinal tract tumors result in MBD in less than 10% of cases.⁷ Tumors are most often found in the proximal half of long bones, following the arterial vascular supply that runs proximal to distal.

Unlike primary tumors, the early diagnosis and treatment of metastatic bone tumors will not result in a cure of the disease, and length of survival following the detection of MBD is limited, regardless of primary cancer type. For example, large, retrospective studies of breast cancer patients have demonstrated mean survival time periods of 22 months (overall), 26 months in patients with bone metastases only, 21 months in patients with bone and visceral metastases, and 18 months with visceral metastases.⁸ The two-year probability of survival for breast cancer patients with bone metastases only is estimated to be 0.74 (95% CI, 0.67 to 0.79) and 0.56 (95% CI, 0.46 – 0.66) for simultaneous bone and visceral metastases.⁹ Further, the presence of multiple metastatic bone lesions predicts shorter length of survival with solitary lesions representing a minority (41%) of detected disease.¹⁰ Unfortunately, breast cancer, when compared to the relatively more lethal lung, thyroid, and kidney cancers, has been cited as having the best median length of survival.¹⁰

The morphology of the tumors in metastatic bone disease may be of blastic, lytic, or mixed type. Cancers of purely lytic or mixed blastic-lytic composition are the most concerning, as they result in local destruction of the cortical bone, functional compromise, and cause significant pain.¹¹ Prophylactic fixation of impending pathological fractures from MBD has demonstrated significant clinical benefit, including less blood loss, faster procedure time, shorter length of hospitalization and higher likelihood of discharge to home⁹, reduction of pain, improvement in activities of daily living, and better quality of life.¹² Importantly, efforts have been made to predict fracture risk and the need for prophylactic fixation based upon the clinical and radiographic features of MBD.

Prediction of Fracture Risk: Mirels Scoring System

The prediction fracture risk in long bones due to MBD began in the 1960's with the efforts of Aufranc^{13, 14} and Bunting.¹⁵ Later efforts by Casadei¹⁶, Harrington¹⁷, and Hipp¹⁸ in the 1980's and 90's improved the lack of statistical rigor in early efforts and the classification characteristics of impending fractures, however no agreement was made between the different efforts. Ultimately, Mirels¹⁹ proposed the rating system that is most widely used today for the assessment of fracture risk.

Mirels scoring system is based upon four characteristics: (1) site of lesion; (2) nature of lesion; (3) size of lesion; and (4) pain. The features of each characteristic are assigned scores of 1 to 3, as shown below:

Table 1				
Mirels' scoring system				
Score	Site of lesion	Size of lesion	Nature of lesion	Pain
1	Upper limb	< 1/3 of cortex	Blastic	Mild
2	Lower limb	1/3–2/3 of cortex	Mixed	Moderate
3	Trochanteric region	> 2/3 of cortex	Lytic	Functional

(Adapted and published with permission of Lippincott Williams & Wilkins from Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res.* 1989;249:256–264.)

Table 1: Mirels' Scoring System

Site of lesion includes three categories: upper extremity, lower extremity, and the peritrochanteric region of the femur.

The histopathological characteristic of the lesion is characterized by increasing score for blastic, mixed, and lytic type. The rate of fracture in these categories was 0%, 32%, and 48%, respectively.¹⁹

The size of the lesion is characterized as an estimated percentage of the cortical thickness. Increasing scores are assigned to values from 1/3, 1/3 to 2/3, and greater than 2/3. The rate of fracture in these categories was 0%, 5%, and 81%, respectively.¹⁹

Functional pain – as defined by the International Association for the Study of Pain – is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or *described in terms of such damage.*” Of the categories of pain assessed, the progression to fracture with functional pain was 100%; mild and moderate pain assessments progressed to fracture in only 10% of cases.¹⁹

Based upon the overall Mirels Score, a prophylactic fixation is indicated with scores of 9 or greater; a score of 7 or less may be managed with analgesia and radiotherapy. The probability of fracture with a score of 8 presents a clinical dilemma, in that only 15% of cases were observed to fracture. Thus, the recommendation was made for prophylactic fixation with heavy emphasis on clinical judgment.¹⁹

The Mirels Scoring System has been independently reviewed and validated multiple times. Most recently, Damron²¹ determined the sensitivity to be 91% with specificity of 35%, being reproducible, valid, and more sensitive than clinical judgment across all experience levels.

In similar fashion, Harrington's¹⁷ scoring system incorporated lesion size and the percentage of local cortical bone destruction in the assessment of fracture risk. In the diaphysis, the greatest risk was for cortical destruction > 50%; in the metaphysis, risk of fracture was greatest at 50 – 75%. By augmenting Mirels' methodology with a minimum acceptance of >50% cortical destruction, irrespective of diaphysis or metaphysis, the false positives encountered in prophylactic treatment with a Mirels score of 8 may be decreased.

Stabilization Practices for Impending and Actual Pathological Fractures

The goals of surgical treatment for impending and actual pathological fractures secondary to MBD are to relieve pain, reduce the need for narcotics, restore skeletal strength, and regain the ability to perform activities of daily living. Long bone surgical stabilization techniques are heavily dependent upon the location and extent of bone erosion, but may be broadly divided into methods employing intramedullary nails with locking pins and screws; extramedullary plates and screws; total joint arthroplasty; or via the direct injection of cement (with or without supplemental hardware stabilization).

Intramedullary Nail Devices

Intramedullary (IM) nail stabilization of an impending fracture is accomplished by inserting a solid metal rod (or "nail") into the medullary canal of the bone, ensuring that the rod length spans the lesion area. The ends of the rod are then fixed in place with locking nails or screws, stabilizing the impending fracture proximally and distally.

IM nails inherently retain certain advantages over plates and screws. Fundamentally, the IM nail is closer to the normal mechanical axis of long bones and acts as a load-sharing device when there is cortical contact, thus subjecting the bone to lower bending forces and decreasing the risk of fracture.²² In MBD, IM nails are attractive as they allow for protection of the entirety of the bone as new lesions may form at a non-contiguous site in the same bone, or the identified lesion may continue to enlarge.²³ IM nails generally involve less soft tissue dissection than plate osteosynthesis, a lower rate of infection, and (theoretically) less risk of local nerve injury.²⁴

Unfortunately, IM nailing is not without shortcomings. IM nail failure – defined as loss of fixation and stabilization – has been reported to be as high as 44% at 60 months survival with a linear increase following implantation.²⁵ Tumor progression, non-union (in fractured bone), surgeon error and hardware failure have been identified as the general mechanisms of IM nail failure, with revision rates being higher in aggressive tumor types, greater-load bearing bones, and more proximal lesions.^{23, 25} Of these categories, surgeon error (improper sizing of the implant, poor location selection for the locking screws), tumor progression (further bone erosion into screw/nail fixation zones), and increasing survival have been identified as primary contributors to failure²⁵⁻²⁷. Sizing error gaps, forced location selection for locking screws in the nail, and greater distribution of the loading area all offer opportunities for improvement with newer technology.

Plates and Screws

The use of interlocking plates and screws for the stabilization of impending pathological fractures is accomplished by using metal plates that span the lesion site, with such geometry that screws are able to be placed in sufficient cortical bone to guarantee purchase and plate adherence.

Plate and interlocking screw systems offer several advantages over IM nails, especially when challenging bone geometry in a confined area is present. For example, with small lesion size and adequate cortical bone present in the distal femur (a challenging anatomic geography), plate and screw systems have been shown to provide equivalent axial stiffness and torsional strength to intramedullary nailing alone.²⁸ Further, anatomically designed plates offer advantages in conforming to surface anatomy, especially the more variable anatomy of the periarticular/trochanteric regions of the humerus, femur, and tibia, where IM nails are subject to greater loading with a higher risk of failure.²⁹

Unfortunately, the success of plates and screw systems vary by anatomic location. In the diaphysis, they have demonstrated higher failure rates than IM nails³⁰; in the peritrochanteric regions, they have demonstrated greater anatomic conformance advantages than IM nails alone, but higher failure rates than partial or total joint prosthesis.^{31, 32} Thus, a significant product gap exists for a device that is anatomically conforming (plates and screws) and also load appropriate (IM nail).

Cementoplasty

“Cementoplasty” broadly describes the percutaneous injection of poly(methyl-methacrylate) (PMMA) bone cement to stabilize the spine and skeletal system³³ alone, or as an adjunct to traditional fixation hardware. Cementoplasty is a broad term, including procedures like kyphoplasty, vertebroplasty, osteoplasty, and sacroplasty, where the role of cement as a gap filler and structural support is indicated.³⁴

The percutaneous injection of poly(methyl-methacrylate) cement for a therapeutic effect was first described in 1987³⁵, where it was successfully used to reduce pain by augmenting vertebral height secondary to compression fracture from a benign neoplasm. Since then, the technique has been widely published upon in the interventional radiology community, and has gained widespread adoption for the treatment of painful vertebral fractures refractory to conservative medical treatment.³⁶⁻³⁸

Cementoplasty has also been widely described in the treatment of fracture and impending fracture secondary to bone pathology – be it osteoporosis, metastatic disease, or neoplasm – where the primary indication is relief of pain³⁹⁻⁴³ and cement is used to increase the strength of fixation⁴⁴ achieved with adjunct hardware. In this setting, pathologic fractures due to lytic MBD present a unique dilemma as they require two products, of which neither is a complete solution: proximal and distal fixation in the setting of compromised bone with an IM rod and locking nails, or the use of cement filler for stabilization of attenuated bone in small lesions.

There is little debate as to the necessity of cement in the treatment of pathologic fractures and impending fractures secondary to MBD. Numerous publications have described the successful use of percutaneous cementoplasty following radiofrequency ablation (RFA) without⁴⁴⁻⁴⁷ adjunctive hardware for small, isolated malignancies, and cement with⁴⁸⁻²⁵ adjunctive hardware for more advanced disease states. In

both applications, significant improvement in stabilization quality, palliation of pain, return of mobility, and quality of life has been described.⁵¹⁻⁵⁴

Similar to plate-screw systems and IM nails, cementoplasty as a technique is limited in application. Small (<25% cortical erosion), solitary lesions of non-load-bearing bones, such as ribs, iliac crest, sternum and clavicle appear to be the most appropriate setting.³³⁻⁵³ In the context of treating impending fractures secondary to MBD, space exists for a device with the length and longitudinal load-sharing properties of an IM nail with complete conformance to the intramedullary canal; the anatomic flexibility of plate-screw systems in variably contoured anatomy and disease types; and the gap filling properties of cementoplasty.

Impact of Impending and Actual Pathological Fractures on Reduction of Pain

Pain reduction following prophylactic fixation of impending pathological fractures and fixation of fractures secondary to metastatic bone disease has been widely studied by the interventional radiology community. To quote Deschamps and de Barre⁵⁴:

“The analgesic benefit of cementoplasty in bone metastases is well-documented in the medical literature as producing a reduction in pain in 80 to 97% of cases.⁵⁰⁻⁵⁷ This benefit is obtained irrespective of the bone site treated, whether vertebrae, long bones or flat bones. Alvarez et al.⁵¹ have shown that cementoplasty of a painful metastatic vertebra produced a significant reduction in pain in 81% of the patients treated (the mean VAS/10 progressing from 9.1 to 3.2) and the possibility of walking again in 77% of patients initially bedridden because of it. Cementoplasty is also very effective for metastatic pain of the long and flat bones, producing a significant improvement in the pain of 91% of patients (the mean VAS/10 progression from 8.7 to 1.9).⁵⁷ This analgesic effect is obtained rapidly, generally between the first and third day following the procedure, permitting early postoperative mobilization of patients and a short hospital stay (24 – 48 hours). The physiological mechanisms of this analgesic effect can as yet be only hypothesized: the effect of the cement stabilizing microfractures and/or the effect of destruction of nociceptive fibers on contact with the cement, through the exothermic reaction generated during its polymerization. According to Urrutia et al.⁵⁸, the mechanical effect takes precedence over the thermal effect since no histological lesions of intraosseous nerve fibers were seen on contact with cement injected into the vertebrae of rabbits. This seems to be confirmed by Anselmetti et al.⁵⁹ who have found identical analgesic efficacy in three groups of patients treated with cements with very different peak polymerization temperatures (group A = 87 °C, group B = 60°C, group C = 45 °C).”

1.2 Rationale for Development of the IlluminOss Photodynamic Bone Stabilization System

According to the Arbeitsgemeinschaft für Osteosynthesefragen/Association for the Study of Internal Fixation (AO) Foundation, there are four guiding principles for successful internal fixation of a fracture: the anatomical reduction of the fracture fragments; stable internal fixation of the bone; the preservation of blood supply; and the ability to facilitate early, active, pain free motion of the associated muscles and joints. These principles guided the development of the IlluminOss Photodynamic Bone Stabilization System (PBSS).

The IlluminOss PBSS may be uniquely suited to meet the needs of fracture fixation and overcome shortcomings of current solutions in pathological fractures by providing longitudinal stability along the length of the device, as with an IM nail, but via a minimally invasive delivery and stabilization technique. To place the device, a small incision is made to insert the device percutaneously into the medullary canal with minimal soft tissue dissection. The non-compliant balloon is then adjusted to span the fracture, and conforms to the patient's unique medullary canal, providing stable internal fixation once inflated with the monomeric cement. After the cement has been hardened by polymerization with visible light, additional hardware (pins and screws) may be used to stabilize the fracture. The location of supplemental hardware – such as pins and screws – is not pre-determined by the device configuration, as with traditional IM nails. This allows the surgeon to independently choose hardware placement, preserving blood supply to the bone, and optimizing the environment for normal biological healing to occur. Obstructive bracing is not required following implantation, and only a small surgical dressing is needed to dress the incision site. Thus, the patient is able to move the affected area following surgery and may potentially begin the return to the pre-fracture level of activity earlier than with traditional technology.

2 Intended Use & Device Description

2.1 Intended Use

The IlluminOss PBSS is indicated for use in fracture repair. It received CE Mark clearance in 2009 for use in the treatment of phalange of the hand, metacarpal, distal radius, radius, ulna, olecranon, clavicle, and fibula fractures. It provides stabilization for these fractures via a minimally invasive technique in which the bone is not subjected to significant weight bearing forces. As of June 2014, the PBSS has been used to treat over 400 bones in patients residing in Chile, United Kingdom, and the European Union. No intra-operative, post-operative, or systemic adverse device events have been reported. The PBSS is not cleared for use in the United States (US). More information regarding device use is provided in Section 3 of the protocol.

This study, conducted under an IDE from the U.S. Food and Drug Administration, will evaluate the use of the PBSS in the treatment of impending and actual pathological fractures of the humerus. The results of this study will be used to support a marketing clearance for the use of the PBSS for pathological fracture of the humerus in the United States.

2.2 Device Description

The IlluminOss PBSS is manufactured by IlluminOss Medical, Inc. (East Providence, Rhode Island); the monomer cement is manufactured by Dymax Corporation (Torrington, CT, USA). The PBSS is comprised of an inflatable, thin walled polyethylene terephthalate (PET; Dacron™) balloon mounted on an insertion catheter. This balloon catheter system is designed to deliver the monomer cement to the fracture site via the medullary canal of the bone.

Once the balloon is in place and has spanned the impending or actual pathological fracture site, the delivery sheath is removed, uncovering the balloon; the balloon is then infused with light-curable monomer cement via a syringe, causing the balloon to expand. The inflated balloon circumferentially fills the medullary canal of the fracture, applying a transverse reduction force and stabilization to the fracture.

The bone is then visualized under fluoroscopy to ensure that the impending fracture or fracture site has been properly spanned and stabilized, with the balloon in the appropriate position, fully-inflated and contacting the inner diameter of the bone.

The light system is then activated, causing the photoinitiator in the monomer to rapidly polymerize and harden the cement *in situ*. The cured balloon thus becomes a bone stabilizing system (or “bone pin”) to aid in the support and healing of the bone fracture by primary callous formation and remodeling.

3 Justification for Clinical Investigation Design

3.1 Pre-Clinical Investigation Results

The individual components of the PBSS and the hardened bone pin were tested under the conditions of the company’s ISO 13485:2003 compliant quality system, as well as domestic and international standards (MDD 93/42/EC-2007).

The liquid monomer, the disposable implant catheter set, and the polymeric bone pin have undergone extensive biocompatibility testing including genotoxicity, cytotoxicity, systemic sub-acute and sub-chronic toxicity, sensitivity and irritation testing, and implant performance evaluations. The pins were tested by an independent laboratory in pre-clinical models under GLP conditions of standard use and failure modes to assess the safety and performance of the implant materials. The results of the panel of testing indicated that the presence of the uncured monomer and cured polymeric bone pin were well-tolerated in animal models, had no negative effect on cell viability, and were not associated with permanent local or systemic complications.

The light source used to deliver visible light to the liquid monomer, the Blue Wave 75 VT Photodynamic Light Box, is similar to a commercially available product used in the UV adhesive industry. Testing of this component was conducted by an independent, certified testing agency, and evaluated all mechanical, electrical, software and user-interface functionalities in compliance with international standard IEC 60601-1, 2nd and 3rd Edition. A standard, commercially available 75-Watt light bulb is used within the unit to transmit light into the lumen of the catheter via a plastic light fiber. The safety and performance of the light output (wavelength and intensity spectrum) have passed all testing conducted by a second independent, certified testing agency.

3.2 Prior Clinical Studies

The PBSS has been cleared for use in the European Union (EU) for the treatment of phalanges of the hand, metacarpal, distal radius, radius, ulna, olecranon, clavicle, and fibula fractures. The ability of the device to perform its intended function in earlier indications is the rationale for performing this investigational study of the PBSS in impending and actual pathological fractures of the humerus secondary to metastatic malignancy.

First-in-Man Study

A First-in-Man feasibility study was conducted in Chile, South America for the use of the device in the treatment of phalange and metacarpal fractures. The study, “IlluminOss Medical Photodynamic Bone

Stabilization Study, Protocol #ILLUM-OUS-2008-001” enrolled 3 subjects from November 2008 until August 2009. Enrollment into the study closed in 2009 with no adverse device effects. Subjects met all inclusion/exclusion criteria and were treated for acute fractures of the metacarpal bone. Subjects returned to the hospital for Day 45, Day 90 and Day 180 follow-up visits. At each visit subjects were assessed for ADEs, clinical healing, and fracture alignment. The subjects completed a Disability of the Arm, Shoulder and Hand (DASH) questionnaire and radiographs were obtained. The Principal Investigator (PI) reported that all subjects were clinically healed by the Day 45 visit, and no local or systemic device-related complications were reported. The study is closed.

EU Registry Study

The EU Registry for the IlluminOss Bone Stabilization System, Protocol # ILLUM-EUREG-2010-001, was initiated in September 2010 and follow-up is ongoing. The aim of the registry is to collect technical and clinical outcomes on treated subjects. The subjects may be followed either until they are discharged from clinical care, or are followed for up to two years post index surgery. There are no pre-specified procedures or additional mandatory visits for subjects enrolled into the registry. Research personnel collect and enter standard of care demographic and fracture-related data, including radiographs, into a web-based database for review by IlluminOss personnel. The database prospectively queries for the incidence of adverse device effects.

Enrollment closed in January 2014. A total of 146 bones have been treated in 131 enrolled subjects at two centers in Germany and four centers in The Netherlands. The device has been used to treat acute fractures and has been used in revision surgeries across indications. It has been used alone, and with supplemental hardware, at the discretion of the surgeon.

Implant Location	TOTAL No. of Subjects Implanted
Metacarpal	14
Fibula	20
Humerus	42
humerus and femur	1
ulna	15
radius	1
distal radius	12
radius and ulna	2
distal radius and ulna	5

Pelvis	4
Tibia	1
tibia and fibula	3
Femur	7
Sternum	1
Unknown	3
Total # of subjects	131

Of the 131 subjects identified above, 23 subjects were available for a post-operative visit six months to two years or more post implant. Out of the 23 subjects, 70% (16/23) had radiographs taken, which were assessed by an independent assessor to evaluate maintenance of reduction, alignment, and radiographic healing. Twelve of the 16 subjects (75%) were treated for index fractures. Radiographic healing, as defined by cortical bridging and $\geq 75\%$ dissolution of the fracture line, was reported for 92% (11/12) of the subjects. Four of the 16 subjects (25%) were treated with an IlluminOss device during a revision procedure. Radiographic healing, as defined above, was reported for 75% of the 16 subjects. No reports of device migration were reported for any subject at any visit. No unanticipated adverse device effects and no clinically significant adverse device effects have been reported.

4 Risks and Benefits

4.1 Anticipated Clinical Benefits

Compared to traditional impending fracture or fracture treatment technologies, subjects may benefit from participating in this study as use of the IlluminOss PBSS will likely result in: (1) shorter operative time; (2) shorter length of hospital stay; (3) fewer narcotic and physical therapy prescriptions; and (4) fewer post-operative complications. Additionally, subjects may benefit from regaining use of their limb earlier than if they were treated with conventional plates, IM rods, or cement alone. It is also possible that subjects may not experience any of these benefits. The results of this study will benefit the medical community treating actual and impending pathological fractures secondary to metastatic bone disease by evaluating the safety and performance of the PBSS.

4.2 Anticipated Adverse Device Effects (Risks)

Adverse events (AEs) that may be anticipated in this clinical study are believed to be similar to and consistent with those associated with impending fractures, fractures, anesthesia, and surgical treatment, including the use of other commercially available plating and intramedullary fixation technologies. Complications may occur at any time during or after device implantation.

Possible risks that may be related to the IlluminOss device are believed to be similar to other types of bone pin devices. As with any IM fixation or plating system, possible risks may include, but are not limited to, the following:

- inability of the device to treat the fracture (maintain alignment and reduction);
- risk of implant fracture when used with screw fixation
- loosening, bending, cracking of the components or loss of fixation in bone;
- loss of anatomic position with non-union or malunion with rotation or angulation;
- the need for a second operation to treat the fracture or to remove the device;
- risk of uncured/cured monomer outside of the intended area, resulting in effects on the surrounding tissues and muscles, and in possible systemic side effects;
- relative increased risk of infection following a foreign body implant;
- x-ray findings of small bone loss (osteolysis) may be observed.

In addition, there is a rare chance that the balloon catheter may become damaged and leak the uncured monomer into the space of the fractured bone prior to the application of the light source to harden the monomer.

Complications associated with surgery and use of anesthesia are always possible, but are not common.

Possible risks of humerus surgery may include, but are not limited to, the following:

- infection;
- permanent numbness or weakness in the area of treatment;
- fractured bones do not heal together properly, or may heal with a bent shape;
- the need for a second procedure, not related to the investigational device
- abnormal bone loss or growth;
- swelling or bruising of tissue;
- thromboembolic event (blood clot or other material that could result in organ damage or failure);
- irregular heart rhythm;
- bleeding, possibly requiring transfusion;
- damage to nerves or blood vessels or muscles, or other tissue.

Possible risks of the use of anesthesia are:

- nausea and vomiting;
- headache;
- backache;
- sore throat or hoarseness;
- muscle soreness.

Other rare side effects or complications of the use of anesthesia include, but are not limited to:

- eye injury/blindness;

- lung complications;
- infection;
- damage to veins or arteries;
- damage to mouth, teeth or vocal chords;
- heart or blood pressure complications;
- brain damage;
- allergic reaction;
- prolonged recovery from anesthesia;
- seizure or stroke;
- nerve damage (including numbness, pain or paralysis);
- awareness or recall of the operation;
- death.

These events could possibly require surgery or other treatment to address the event.

4.3 Residual Risks Associated With the Investigational Device

There are no known residual risks associated with the use of the investigational device.

4.4 Risks Associated With Participation in the Clinical Investigation

Risks associated with participation in the investigation include additional radiographic assessments that may not be standard of care in the follow-up of traditional impending fracture treatment surgery. Enrolled subjects will have standard of care radiographs taken at the Day 7-14, 30, and Day 90 visits. Depending on the research site, the Day 180 and 360 radiographic assessments may not be considered standard of care. The risk of exposure to extra radiation at these time points is expected to be less than that received during a routine airplane flight.

4.5 Risk Mitigation

Risks will be minimized by ensuring that only board-certified orthopedic surgeons trained in the use of the IlluminOss PBSS participate as investigators in the study. Strict patient inclusion and exclusion criteria will be followed, enrolling only patients who meet criteria and provide written informed consent. During each follow up visit, subjects will be assessed for AEs, with particular attention to events that may be related to the surgical procedure and the investigational device. Medical monitoring will be conducted to review the frequency, severity, and relatedness of AEs. In addition, the study will be monitored to ensure compliance with the protocol and the continued acceptability of the investigator and institution.

4.6 Risk to Benefit Rationale

The potential benefits to enrolled subjects and the medical community outweigh the potential risks identified in this protocol. Robust preclinical testing has demonstrated the safety of the device components and all materials that come in contact with enrolled subjects. The early experience of the PBSS in CE Marked indications suggest the device is well tolerated and performs its primary function of

providing stabilization and alignment to fractured bones. This study has been designed to provide frequent safety assessments and to identify any potential new risks.

5 Study Objectives

The primary objective of the study is to collect safety and performance data of the PBSS when used for the treatment of painful impending and actual fractures of the humerus secondary to metastatic malignancy.

6 Study Design

This is a prospective, multi-center, open label study to evaluate the PBSS in the treatment of impending and actual pathological fractures of the humerus for the purposes of FDA marketing clearance.

A total of up to 80 subjects will be recruited from up to 20 sites in the United States .

6.1 Study Endpoints

The following study endpoints will be evaluated in all subjects who consent to the study and are treated with the IlluminOss PBSS. All endpoints are subject-based unless otherwise specified.

6.1.1 Primary Endpoint

Pain Reduction

- Change in VAS Pain Score at Day 90

Functional Improvement

- Change in Revised Musculoskeletal Tumor Society Rating Scale for Upper Extremity (MSTS) at Day 90

Primary effectiveness will be evaluated relative to literature-based historical controls. These were selected on the basis of comparability to the target population and similarity to the investigational device. There are two primary effectiveness endpoints, reduction in pain at 90 days relative to pre-treatment baseline and improvement in function at 90 days relative to pre-treatment baseline. The changes in VAS pain and MSTS from pre-treatment baseline to day 90 will be involved in the primary effectiveness tests to be applied to enrolled patients who have actual or impending fractures, with VAS pain scores of at least 60mm. Non-inferiority of mean changes over time will be compared relative to reference values determined through evaluation of historical controls. Testing for VAS pain reduction will first be performed. Only if the null hypothesis of inferiority in mean VAS pain improvement is rejected at $p < 0.05$, will the co-primary endpoint MSTS be similarly tested.

Safety Success is evaluated according to a composite endpoint by meeting all of the following criteria:

- Clinical
 - No Serious Device Related Complications
 - No additional surgical interventions:

- Revisions, supplements, fixations, or removals
- Radiographic
 - No device fracture, migrations, mal-alignment or loss of reduction or fixation

The number and percentage of patients achieving the Safety Success endpoint will be reported cumulatively for day 7-14, 30, and 90 and 180 and 360 and with 95% 2-sided exact binomial confidence intervals.

6.1.2 Secondary Endpoints

The secondary endpoints, evaluated at the Day 90 Visit, include:

- The individual components of the safety endpoint
- Other secondary endpoints include:
 - Duration of index procedure and length of hospital stay
 - Activities of Daily Living score through all follow-up intervals
 - Disability status
 - Evaluation of duration of physical therapy prescription
 - Assessment of prescription and over-the-counter analgesic medication use
 - Survivability from time of index procedure to death

The safety endpoints evaluated through Day 90 also include:

1. Incidence and number of AEs.
2. Incidence and number of procedure- and device-related complications.

The secondary endpoints and safety endpoints listed above will also be examined during the extended follow up portion of the trial at Day 180 and 360.

6.2 Primary Effectiveness Hypothesis

The primary effectiveness hypotheses for the primary VAS pain improvement endpoint and the co-primary MSTS functional improvement endpoints are as follows:

H_0 : mean improvement in VAS at 90 days \leq 80% of Ref. (inferior)

H_a : mean improvement in VAS at 90 days $>$ 80% of Ref.(not inferior)

H_0 : mean improvement in MSTS at 90 days \leq 80% of Ref. (inferior)

H_a : mean improvement in MSTS at 90 days $>$ 80% of Ref (not inferior)

Testing for pain reduction will first be performed. Only if the null hypothesis of inferiority in mean VAS pain improvement is rejected at $p < 0.05$, will the co-primary endpoint MSTS functional improvement be similarly tested. P-values will be determined by comparing the maximum likelihood estimates of average mean at 90 days to target value determined through evaluation of historical controls based on the mixed model for repeated measures (MMRM) described below.

6.3 Historical Controls

VAS pain improvement: Target reference mean improvements were derived from literature-based historical control data available on a per patient basis from 4 selected articles (Gregory et al. 2011, Kim et al. 2011, Deschamps et al. 2012, and Pretell et al. 2010). The minimum improvement in Pretell and Kim were both 40. The Pretell study reported mean improvement of (SD) = 74.8 (13.3) in 21 patients and the Kim study provided mean (SD) improvement of 56.7 (11.1) in 15 patients. Gregory included patients with actual fractures and impending fractures. Four patients had baseline pain scores of zero and 1 had a score of 20; all remaining patients had baseline VAS ≥ 40 . Mean (SD) improvement for patients with baseline VAS pain ≥ 40 mm was 67.5 (16.7). Kim and Gregory used 10 point numerical rating scales and these were multiplied by 10 to put measurements on the same scale as Pretell. The following table summarizes the improvements in VAS pain score these 44 patients by study.

Level	Means and Std Deviations			
	Number	Mean Impr	Std Dev	Std Err Mean
Deschamps	8	67.50	16.69	5.90
Kim	15	56.67	11.13	2.87
Pretell	21	74.76	13.27	2.90

Mean improvements significantly differed among studies based on one-way ANOVA $F(2,41)=8.15$, $p=0.001$ due to differences in timing of assessments and other study conduct differences. However, it is clear that there were very large mean improvements in all three studies. Moreover, the SD's are similar across studies providing confidence in the estimated between patient variance. The weighted mean improvement is 67.3 and the pooled estimate of the SD is 13.3. To determine reference target for the primary test of non-inferiority, the weighted mean improvement was multiplied by 80% to get 53.8. Therefore, the primary effectiveness hypothesis concerning VAS pain improvements is:

H_0 : mean improvement in VAS at 90 days ≤ 53.8

H_a : mean improvement in VAS at 90 days > 53.8

That is, this study seeks to demonstrate that the mean change improvement in VAS pain scores from baseline to Day 90 is greater than 53.8. Clearly, a mean improvement >53.8 is clinically meaningful and important to patients. If this is demonstrated, it will be concluded that the investigational device performance is not clinically significantly inferior to the historical control as defined above.

MSTS Improvement: The Kim article and the Gregory article contain data for improvements in MSTS. However, the intervention in the Kim article was more similar to the investigational device (i.e., intramedullary nail). It was also not possible to determine timing of post-operative MSTS assessments in Gregory. Therefore, reference target for MSTS improvement was constructed using the Kim study as the historical control.

Level	Means and Std Deviations			
	Number	Mean Impr	Std Dev	Std Err Mean
Kim	15	29.55	20.82	5.38

The values of the MSTS range from 0 to 30. The values have been divided by 30 and multiplied by 100% to facilitate interpretation. The standard deviation of mean improvements is somewhat larger for MSTS compared to VAS pain, implying that a larger sample size is needed compared to VAS pain. 80% of 29.6 is 23.7.

Therefore, the primary effectiveness hypothesis concerning MSTS functional improvements is:

H_0 : mean improvement in MSTS at 90 days ≤ 23.7

H_a : mean improvement in MSTS at 90 days > 23.7

That is, it must be demonstrated that the mean improvement from baseline to Day 90 is greater than 23.7. This implies that the mean improvement must be shown to correspond to nearly 25% of the range of the MSTS scale to meet the effectiveness study success criterion for the co-primary endpoint.

6.4 Subject Population

The investigation population consists of skeletally mature adults, suffering from pain due to impending and actual pathological fractures of the humerus secondary to confirmed metastatic malignancy. Patients meeting the following eligibility criteria will be included.

6.4.1 Inclusion/Exclusion Criteria

General Inclusion Criteria

1. Skeletally mature adult males and females 18 years of age or older.
2. Impending or actual pathological fracture of the humerus, secondary to metastatic bone disease.
3. Females: neither pregnant nor intending to become pregnant during the course of the study, defined as:
 - a. Postmenopausal for at least 1 year OR
 - b. Documented oophorectomy or hysterectomy
 - c. Surgically sterile OR
 - d. If of childbearing potential, must be practicing double-barrier method of birth control, be willing to avoid pregnancy for the period of study participation and have a negative pregnancy test at screening
4. Patient, or his/her legally authorized representative, is able to understand and provide informed consent.
5. Willing and able to comply with post-operative treatment protocol and follow-up visit schedule.
6. VAS Pain Score ≥ 60 mm on 100mm scale.

Impending Fracture-Specific Inclusion Criteria

7. Documented presence of at least one metastatic lesion of the humerus.
8. Mirels Criteria Score ≥ 8 . (specific to the target humeral lesion and subject to minimum VAS score requirements)
9. Destruction of cortical bone at impending fracture site $> 50\%$.

Actual Fracture-Specific Inclusion Criteria

10. Fracture is closed, Gustilo Type I or II.

General Exclusion Criteria

1. Primary tumor (osteogenic origin, etc.) at site.
2. Impending or actual fracture at any other location, that, in the Investigator's opinion, would preclude ability to assess pain and/or function in the target humerus
3. Active or incompletely treated infections that could involve the device implant site.
4. Distant foci of infection that may spread to the implant site.
5. Allergy to implant materials or dental glue.
6. In the investigator's judgment, functional deficit in the target humerus with an etiology other than bone metastases (e.g. due to vascular insufficiency).
7. In the investigator's judgement, focal neurologic deficit as a result of metastases in the brain, spine, or other central nervous system disorders.
8. Uncooperative patients, or patients who are incapable of following directions (for example, as a consequence of a neurological or psychiatric disorder).
9. Prisoner.

Impending Fracture-Specific Exclusion Criteria

10. Mirels Score < 8 (specific to target humeral lesion).
11. Destruction of cortical bone at impending fracture site < 50%.
12. Prior surgery and/or prior fracture of affected site.
13. Any articular component to impending fracture site.

Actual Fracture-Specific Exclusion Criteria

14. Open fractures with severe contamination.
15. Extremely comminuted fractures where insufficient holding power of the balloon on the intramedullary canal is probable.
16. Patients whose intramedullary canal at site of fracture measures smaller than the diameter of the sheath provided.

6.4.2 Criteria and procedures for subject withdrawal or continuation

6.4.2.1 Conditions for Discontinuation

The PI may prematurely discontinue any subject's participation in the study if the PI feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. Once the subject has been enrolled in the study, the subject may withdraw consent to participate in the study at any time without prejudice. Participation in this clinical investigation is entirely voluntary.

6.4.2.2 Data Collection and Follow-up for Discontinued Subjects

If a subject prematurely discontinues from the study, the reason for study termination will be recorded, if available. All reasons for termination will be categorized and tabulated by number and percent. If termination was the result of an AE or death, completion of the appropriate AE forms and/or notifications will ensue. Whenever possible, an exit/final visit examination will be conducted prior to termination from the study. If possible, permission for contacting the subject for the assessment of long-term outcomes will be obtained.

6.4.2.3 Subjects Lost to Follow-up

All reasonable efforts will be made to obtain complete data for all subjects. Missed observations may occur when subjects are lost to follow-up or when subjects demonstrate noncompliance with the required assessments. Subjects are considered lost to follow-up if the site is unable to locate the subject despite documented attempts to locate the subjects via two telephone calls and a certified letter.

6.4.3 Enrollment

The study will be described to skeletally mature adult males and females presenting with a painful impending or actual pathological fracture of the humerus, secondary to metastatic malignancy. If the subject expresses a desire to be in the study, the informed consent process will be initiated.

A subject is considered enrolled in the clinical investigation after the following two conditions are met:

- The patient has provided informed consent
- The sheath assembly used to guide the balloon in place within the intramedullary canal has entered the body

Patients who fail one or more of the eligibility criteria prior to this point are considered screening/enrollment failures and should not be enrolled in the study.

6.4.4 Duration of the Study

The enrollment period is expected to be approximately 12 months. Subjects will be followed for 90 days after treatment and then followed in an extended follow up phase for up to 360 days.

6.4.5 Number of Subjects

80 subjects will be enrolled in the study.

6.4.6 Vulnerable Population

The subject population of this clinical investigation does not meet the criteria for a vulnerable population as defined in 45 CFR Part 46. If a subject loses ability to consent during the course of the study this will lead to study exit. Data collected up the point of consent revocation may be used. No data collected after the point of consent revocation will be used. Such subjects will be followed on safety parameters for the course of the study

7 Statistical Methods

7.1 General Methods

This section summarizes key aspects of the analysis plan including the methods to be used to test the primary effectiveness hypothesis and justification for the sample size to be used in these tests. Additional details regarding methods for the final data analysis will be provided in a separate Statistical Analysis Plan (SAP) which will be written and approved prior to study launch with any amendments approved prior to database lock. The SAP will detail all analyses and data displays. The SAP will be executed according to SOPs in a controlled environment.

All statistical analyses will be performed using SAS for Windows, Version 9.2 or higher. Descriptive statistics for continuous variables will consist of the number, mean, standard deviation, minimum, median, and maximum values. For categorical variables, the count and percent of each category will be displayed.

7.2 Sample Size Rationale

VAS pain improvement: The primary endpoint is change in VAS from baseline to Day 90. All patients will be included in the primary analysis of this endpoint through the use of a mixed model repeated measures (MMRM) model assuming an unstructured covariance matrix. To be conservative, statistical power is evaluated on the basis of a single-sample t-test with a 1-sided $\alpha=0.05$ based on the change at Day 90. As discussed in Section 6.2 above, the null and alternative hypotheses of interest are:

$$H_0: \text{mean improvement in VAS at Day 90} \leq 53.8$$

$$H_a: \text{mean improvement in VAS at Day 90} > 53.8$$

Based on the above historical control data in Section 6.2, an estimate of the standard deviation of the primary endpoint is 13.3. Under the assumption this is the true standard deviation, under the assumption the true mean improvement from baseline VAS at Day 90 is 58, then 68 evaluable patients yields over 80% power to reject the null hypothesis in favor of the alternative. In order to account for 15% premature withdrawal rate, a total of 80 patients will be enrolled. Note that the assumption of 58 for the true mean improvement from baseline VAS at 90 days may be conservative given the historical control data in Section 6.2 (where the overall mean change was estimated to be approximately 67, over a shorter periods than 90 days).

MSTS improvement: The second primary endpoint, to be tested if the above null hypothesis for improvement in VAS is rejected, is change in MSTS from baseline at Day 90; this will be analyzed a similar MMRM manner as the primary endpoint above. As discussed in Section 6.2 above, the null and alternative hypotheses of interest for this endpoint are:

$$H_0: \text{mean improvement in MSTS at Day 90} \leq 23.7$$

$$H_a: \text{mean improvement in MSTS at Day 90} > 23.7$$

The hypothesis regarding mean improvement in MSTS will be tested conditionally on rejection of the null hypothesis concerning VAS pain improvements (1-sided $p<0.05$). Based on a single-sample t-test (1-sided $\alpha=0.05$), assuming that the true standard deviation at each visit is equal to 20.8, assuming a sample size of 68 (accounting for potential LTF), then at least 80% power will be achieved to reject the null hypothesis that the

mean improvement in MSTS <23.7 if the true mean change is at least 30.3 at Day 90. This value is similar to the mean improvement for the Kim historical control (mean = 29.6). Thus, as long as the true mean improvement across post-baseline visits is similar to than the mean improvement reported in Kim, there will be good statistical power to reject the conditional hypothesis concerning the co-primary endpoint of improvement in upper arm function as reflected in change in MSTS at Day 90.

7.3 Analysis Population

The Intent-to-Treat (ITT) analysis population is defined as all subjects who provide informed consent, undergo surgery, and have an implantation or attempted implantation of the IlluminOss Photodynamic Bone Stabilization System into the intramedullary canal; this includes subjects for whom implantation of the IlluminOss device is attempted but fails; such patients will be followed and included in the ITT population. The ITT population is equivalent to the Full Analysis Set (FAS). The ITT population will serve as the primary analysis population. Effectiveness will be evaluated in the ITT population as primary.

The per-protocol (PP) analysis population is defined as all ITT subjects who achieved the 90-day visit. This will be the secondary analysis population.

7.4 Demographic and Baseline Characteristics

Summary tables will be provided for demographic and baseline characteristics including age, sex, race, ethnicity, work status, occupation, history of pain, smoking history, hand dominance, and fracture characteristics if evident. Continuous variables will be summarized using means, standard deviations, medians, minimum, and maximum values.

7.5 Analysis of Primary Endpoint

The primary effectiveness hypotheses to be tested in this study are:

H₀: mean improvement in VAS at Day 90 \leq 80% of Ref. = 53.8

H_a: mean improvement in VAS at Day 90 > 80% of Ref. = 53.8

H₀: mean improvement in MSTS at Day 90 \leq 80% of Ref. = 23.7

H_a: mean improvement in MSTS at Day 90 > 80% of Ref. = 23.7

Testing for VAS pain reduction will first be performed. Only if the null hypothesis of mean VAS pain improvement is rejected at one-sided 0.05 level of significance, will the co-primary endpoint concerning MSTS functional improvements be similarly tested.

Summary statistics for VAS and MSTS scores at baseline and changes from baseline to each follow-up visit will be presented (mean, standard deviation, median, minimum, and maximum values).

Each null hypothesis will be tested as follows: A mixed model repeated measures (MMRM) model will be executed for the dependent variable of “change from baseline at each visit”, with the categorical main effect of visit (Day 7-14, Day 30, Day 90) as the independent variable. From this model, the estimate of the overall mean change from baseline at Day 90 and its standard error, will be established, and from this a one-sample t-test will be generated to test the null hypothesis of interest at a one-sided 0.05 level of significance. The MMRM model

will be estimated using a direct likelihood approach as implemented in the SAS procedure PROC MIXED. The model will include the baseline value of the score as an additional covariate. The model is designed not only to account for correlations among responses over time, but to use these correlations to implicitly impute missing values from the non-missing values. Inferences based on this approach are unbiased under the assumption of MAR (missing at random) which is a more generally true assumption than MCAR (missing completely at random)⁶⁵. The MMRM will employ an ‘unstructured’ covariance matrix that allows the correlations to vary between each pair of time points and allows the variances to differ over time. If the model does not converge with the unstructured covariance matrix, other structures may be used, starting with compound symmetry. Full details will be provided in the formal statistical analysis plan.

These analyses will be carried out for the ITT (primary) and PP (secondary) analysis sets.

7.6 Handling of Missing Data

All patients in the ITT analysis set will be included in the primary effectiveness test as long as there are non-missing baseline values. The MMRM provides implicit imputation of missing post-baseline values through the covariance matrix reflecting the associations among responses within patient over time.

7.7 Multiplicity

The primary effectiveness hypothesis concerns improvements in VAS pain at Day 90. Only if the null hypothesis is rejected relative to historical control with $p < 0.05$ will testing for improvement in MSTs function occur. Pre-specification of the order of testing within this hierarchical framework eliminate type 1 error inflation due to multiplicity. Therefore, no multiplicity adjustment will be made across the co-primary endpoints.

7.8 Analysis of Secondary Endpoints

7.8.1 Procedure- and Device-related Complication Rate

The numbers and percentages of subjects who experience a procedure- or device-related complication by the Day 90 Visit will be presented along with the corresponding 95% binomial confidence intervals.

7.8.2 Duration of Index Procedure and Length of Hospital Stay

Descriptive statistics for duration of index procedure and length of hospital stay will be presented including mean, standard deviation, median, minimum, and maximum values.

7.8.3 No Pain at Palpation

The numbers and percentages of subjects with no pain at palpation will be presented at each follow-up visit.

7.8.4 MSTs Upper Extremity Functional Outcome

The Musculoskeletal Tumor Society Revised Functional Score will be assessed pre- and post-operatively to evaluate functional outcome. Summary statistics for the MTST function score will be pre-operatively and at each

follow-up visit as will changes from baseline using means, standard deviations, medians, minimum values, and maximum values.

7.8.5 Disability Status

The numbers and percentages of subjects who are considered disabled, per Investigator assessment, will be presented at each visit where disability status is collected.

7.8.6 Range of Motion

Range of motion will be assessed using ordinal variables reflecting the forward flexion, lateral elevation, external rotation, and internal rotation of the arm. Summary statistics for range of motion will be presented at each follow-up visit. In addition, the number and percentage of subjects for each level of these ordinal variables will be displayed.

7.8.7 Return to Work

The numbers and percentages of subjects who returned to work, and in what capacity (e.g., full-time, part-time, with limitations) will be presented at each follow-up visit.

7.8.8 Extended Follow Up Visits

The analysis described above will also be provided for the extended follow up visits once completed.

7.8.9 Adverse Events

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Incidences of treatment-emergent AEs (TEAEs) will be presented. Incidences of TEAEs will also be presented by maximum severity, seriousness, and relatedness (device or procedure related) at Day 90 and during the extended follow up visits. This includes the reporting of device revisions, reoperations, removals, supplemental fixations, or other procedures.

7.9 Optional Analyses

7.9.1 Fracture Location/Type of Primary Cancer

Analysis of primary and/or secondary endpoints as described above may also be performed on subgroups. These subgroups would be defined by fracture location (proximal, diaphyseal and distal fractures) and by type of primary cancer.

7.9.2 Health Economic Data

Descriptive statistics for the duration of physical therapy prescription will be presented. The number and percentage of subjects who used supportive orthopedic devices post-surgery and who used prescription and over-the-counter analgesic medication will be presented. No formal statistical testing will be undertaken and no p-values will be presented.

7.10 Interim Analysis

After 30 patients have been treated and followed for 90 days, an interim MMRM analysis on change from baseline VAS at Day 90 will be carried out. The purpose of this interim analysis is not to stop the trial for overwhelming efficacy, but rather to (a) potentially stop for futility; and (b) potentially increase the sample size if the mean VAS improvement from baseline at Day 90 is large but not as large as anticipated in the original sample size calculations. The interim analysis will be generated and reviewed by an independent statistician not otherwise involved in the study, who will report to the Sponsor of whether or not a sample size increase is needed, but with no other details regarding the interim results.

At this interim stage, the conditional power for rejecting the above null VAS hypothesis will be calculated, conditioned on the interim observed results. If the conditional power is $\geq 80\%$, the study will continue as is. If the conditional power is between 50% and 80%, then the sample size increase required to achieve 80% conditional power will be calculated using the Chen-DeMets-Lan (CDL) approach³. If conditional power is between 10% and 50%, no sample size increase will be carried out, and if the conditional power is $<10\%$, the study may be stopped for futility.

Under the CDL approach, an “alpha-penalty” does not need to be made for any sample size increase as long as the maximum sample size increase required to maintain 80% power is below the bound $100 \cdot R\%$ of the original sample size, where R is calculated as follows:

$$\sqrt{1+R}(\sqrt{1+R}-1)/\sqrt{1+R-t} = 0.84/1.645$$

where t is the proportion of information at the interim analysis ($t=0.5$), 0.84 is the standard normal (z) critical value corresponding to 80% power, and 1.645 is the z critical value corresponding to a one-sided alpha of 0.05. Specifically, as long as the sample size increase required to maintain 80% conditional power is $<R \cdot 100\%$ of the original sample size, then the sample size increase does not require an alpha-penalty.

8 Schedule of Subject Activities

8.1 Visit 1: Screening and Baseline

8.1.1 Screening

A Pre-screening Log will show 1) all patients (anonymized) who presented with an impending pathological fracture or actual fracture but who were not offered the study and the reason(s) and 2) all patients to whom the study was described but who declined participation.

Qualified patients who agree to participate in the study will be required to sign an informed consent form (ICF). After signing the ICF, study subjects will undergo study-specific screening procedures.

All patients who consent to the study will be listed on the Screening/Enrollment Log. This log will document the date of screening, the results of screening, and the primary reason for exclusion if the subject did not satisfy the initial eligibility criteria or was disqualified during surgery.

8.1.2 Baseline

The following will be performed after the subject has signed an ICF:

A clinical assessment will be performed as follows:

- Inclusion and exclusion criteria review;
- Relevant medical history, including smoking history, osteoporosis history, work status, and whether the patient has any disabilities, with a focus on the impending fracture site;
- Physical exam, with focus on target limb, including neurovascular exam, including radiographic assessment and Mirels scoring of the impending pathological fracture;
- Urine pregnancy test (if applicable);
- Current concomitant pain medication use;
- Patient-completed pain VAS;
- Standard of care radiographs of target impending or actual fracture prior to signing consent form;
- MSTs Functional Score and EORTC QLQ-BM22; and
- Optional health economics assessments.

The procedures required for Screening and Baseline may be conducted during more than one visit, provided that all procedures are conducted prior to index treatment.

8.2 Visit 2: Surgery and Post-index Procedures/Discharge

At the time of surgery, should the surgeon discover the presence of a condition that would render the subject ineligible for study participation, the subject will not be treated with the IlluminOss device. The subject should receive the standard of care as determined by the surgeon.

The Instructions for Use (IFU) outlines the full procedure for implantation of the IlluminOss device, along with the device preparation guidance.

Non-medical sponsor representatives and/or designees may be present during the procedure to provide technical assistance to the investigator.

If a bone defect exists, this defect must be measured to confirm eligibility prior to insertion of the IlluminOss PBSS.

*Note: The use of materials to promote bone fusion (i.e., bone graft, bone growth stimulators, etc.) during the index procedure is **prohibited**.*

The following information will be collected during Visit 2:

- Date of surgery;
- Duration of procedure;

- Fracture treatment information (including IlluminOss device lot number and size of device used);
- AE assessment;
- Use of pain medications;
- Physical therapy prescription(s);
- Return to pre-fracture mobility;
- Date of discharge.

Note: If placement of the IlluminOss PBSS is attempted but not successful, the subject will receive the standard of care as determined by the surgeon. This subject will still be part of the ITT population and followed for safety.

If available, health economic data may be obtained. The subject's billing information relating to the surgical procedure (i.e., operating room time, length of stay, medications), follow-up visits, rehabilitation, and other related procedural costs may be collected.

Post-index Procedure Clinical Considerations

Standardized post-operative management will be conducted for all subjects. The post-operative management schema is found in Appendix 13.3.

*Note: Bone growth stimulators (biological, electrical, ultrasound, or magnetic) are **prohibited**.*

Visits 1 and 2 may occur during the same day if acute stabilization of the impending fracture is required. This is at the discretion of the PI. It should be noted that obtaining informed consent should always be done prior to performing any study-specific procedures.

8.3 Follow-up Visits and Evaluations

Follow-up evaluations will be scheduled for 7-14, 30, 90 days post-index procedure and the extended follow up at 180 and 360 days post-index procedure.

8.3.1 Visit 3: 7-14 day Follow-up (+ 3 days)

The following will be performed:

- AE assessment;
- Concomitant/pain medications;
- Subject-completed pain VAS;
- MSTS Functional Score and EORTC QLQ BM22;
- Clinical assessments that include, but are not limited to, assessments for pain, return to baseline mobility, range of motion, return to work, disability status, use of pain medication, and physical therapy prescription status; and
- Radiographs of treatment site (A/P and Lateral)

If available, additional health economic data may be obtained.

8.3.2 Visit 4 and 5: 30-day Follow-up (\pm 7 days) and 90-day Follow-up (\pm 14 days)

The following will be performed:

- AE assessment;
- Concomitant/pain medications;
- Subject-completed pain VAS;
- MSTS Functional Score and EORTC QLQ BM22;
- Clinical assessments that include, but are not limited to, assessments for pain, return to baseline mobility, range of motion, return to work, disability status, use of pain medication and physical therapy prescription status; and
- Radiographs of treatment site (A/P and Lateral)

If available, health economic data may be obtained.

8.3.3 Extended Follow Up Visits 6 & 7: 180-day Follow-up (\pm 30 days) and 360-day Follow-up (\pm 30 days)

The following will be performed:

- AE assessment;
- Concomitant/pain medications;
- Subject-completed pain VAS;
- MSTS Functional Score and EORTC QLQ BM22;
- Clinical assessments that include, but are not limited to, assessments for pain, return to baseline mobility, range of motion, return to work, disability status, use of pain medication and physical therapy prescription status; and
- Radiographs of treatment site (A/P and Lateral)

If available, health economic data may be obtained.

8.4 Activities Performed by Sponsor Representatives

One or more non-medical representatives of the sponsor may be present during implantation of the device.

9 Adverse Events, Adverse Device Effects and Device Deficiencies

9.1 Definitions

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether it is considered device related or not. Only adverse events which are new or have worsened will be evaluated in the safety assessment.

The severity of the AE should be assessed based on the following definitions:

- Mild: an AE that is noticeable to the patient and may require additional therapy;
- Moderate: an AE that interferes with the patient's activities and requires intervention or additional therapies;
- Severe: an AE that is intolerable, or necessitates additional therapy, or places the patient at immediate risk of harm.

Serious Adverse Event: An AE is considered serious (SAE) if it

- results in death,
- led to serious deterioration in health that either:
 - resulted in life-threatening illness or injury, or
 - required in-patient hospitalization or prolongation of existing hospitalization, or
 - resulted in a permanent impairment of a body structure or a body function, or
 - Resulted in medical or surgical intervention to prevent life threatening illness, or
 - led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note that planned hospitalization for a pre-existing condition or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

Device Deficiency: A device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Unanticipated Adverse Device Effect (UADE): an AE is considered to be a UADE if there is an occurrence of an adverse effect on health or safety, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or if any other unanticipated problem associated with the device occurs that relates to the rights, safety or welfare of patients.

Device-related AE: an AE is considered to be device-related when, in the judgment of the PI, the clinical event has a reasonable time sequence associated with use of the investigational device and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the device directly caused or contributed to the AE.

Procedure-related AE: an AE is considered to be procedure-related when, in the judgment of the PI, it is reasonable to believe that the event is associated with the device implant or removal procedures and is not specific to the investigational device used. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

For purposes of this study, the following events are not considered to be AEs because they are normally expected to occur in conjunction with the device-implant and/or removal procedures, or are associated with customary, standard care of patients undergoing surgical procedures for treatment of arm fractures:

- Early post-operative pain (within 72 hours post-index procedure) at the access site and/or related to position on procedure table;
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 hours post-index

- procedure);
- Electrolyte imbalance without clinical sequelae following index procedure, even if requiring correction;
 - Systolic or diastolic blood pressure changes that do not meet the definition of hypotension or hypertension;
 - Low grade temperature increase (≤ 38.3 °C / ≤ 101 °F) within 24 hours of index procedure;
 - Hematocrit decrease from baseline, but not associated with hemodynamic changes and remaining above 30%;
 - Blood loss without transfusion, associated with a decrease in hemoglobin or hematocrit of < 2 g/dl or $< 6\%$, respectively from baseline level with a resulting hematocrit that is $\geq 30\%$ (or hemoglobin ≥ 10 g/dl);
 - Minor, localized tenderness, swelling, induration, oozing, etc. at the surgical site.

This listing of events is intended to provide guidance to the investigational sites for purposes of AE reporting. The PI at the investigational site should utilize his/her own clinical judgment in evaluating subject AEs, and may determine that the above events should be reported as AEs.

The PI should follow all unresolved SAEs until the events are resolved or the investigator assesses them as chronic or stable, the subject is lost to follow-up, the subject has withdrawn consent, or the AE is otherwise explained.

9.2 Relation to the Device and Procedure

The potential relationship of the event to the investigational device or procedure is to be determined by the PI and will be based on the following definitions:

Not related

An AE for which sufficient information exists to indicate that there is no causal connection between the event and the device or procedure. The AE is due to, and readily explained by, the subject's underlying disease state or is due to concomitant medication or therapy not related to the use of the device or the procedure. In addition, the AE may not follow a reasonable temporal sequence following the treatment procedure.

Possibly related

There is a reasonable possibility that the AE may have been primarily caused by the device or procedure. The AE has a reasonable temporal relationship to the use of the device or the procedure and follows a known or expected response pattern to the investigational device or procedure, but alternative etiology is equally or more likely, compared to the potential relationship to the use of the device or the procedure.

Probably related

There is a reasonable probability that the AE may have been primarily caused by the device or procedure. The AE has a reasonable temporal relationship to the use of the device or the procedure and follows a known or expected response pattern to the investigational device or procedure.

Definitely related

The AE has a strong causal relationship to the device or procedure. The AE follows a strong temporal relationship to the use of device or the procedure, follows a known response pattern to the investigational device or procedure, and cannot be reasonably explained by known characteristics of the subject's clinical state or other therapies.

9.3 Reporting to Sponsor

All AEs classified as SAEs, or UADEs shall be reported by the PI (or designee) to the study CRO via telephone 1-215-616-3096 or email (icon-mads@iconplc.com) within 24 hours of learning of the AE.

The PI (or designee) shall send a written report, including a narrative description of the SAE/UADE, to the Sponsor or CRO, within 3 working days of the initial report.

Subject death during the study must be reported by the PI (or designee) with written documentation by facsimile to the Sponsor or CRO within 24 hours of the PI's knowledge of the death. Notification of death must include a brief statement of the relevant details of the death and is required to be signed by the investigator. A copy of the death records, death certificates, and an autopsy report (if performed) should be sent to the Sponsor or the Sponsor's authorized representative (CRO) within 10 days post-autopsy.

In the event of death, efforts should be made to perform an autopsy in order to assess the state of the target arm. If autopsy is not performed, written documentation from the PI will be required regarding the reasons why.

9.4 Reporting to Institutional Review Board and FDA

All SAEs (including deaths), and/or UADEs shall be reported to the IRB and FDA in accordance with regulatory requirements.

For the purpose of this guidance and based on the definitions above, the following events are considered reportable events:

- any serious adverse events
- new findings/updates (e.g. outcome) in relation to already reported events
- any Unanticipated Adverse Device Effects

Events will be reported to the FDA as required by regulation.

The Sponsor (or its representative) shall ensure that SAEs are reported to the Institutional Review Board according to the local requirements.

9.5 Adverse Event Reporting

All AEs, regardless of their relationship to the investigational device, must be recorded on the AE case report form (CRF) by the PI (or designee) for all events that occur after the consent form is signed. Adverse events will be collected based upon medical diagnosis and not symptoms. The report should include: severity, duration, treatment used, treatment outcome, and the PI's written medical judgment of the relationship of the AE to the study device, procedure, , etc. (i.e., unrelated, related, or relationship unknown). In the case of serious or unanticipated AEs, medical record documentation (e.g., procedure notes, discharge summary, relevant progress notes, imaging, or laboratory studies) must be sent to the Sponsor or designee to describe the treatment, duration, resolution, and outcome of the AE.

The following criteria must also be adhered to by the PI:

- Use separate AE form(s) to document each series of events;
- The AE form(s) must be signed by the PI or sub-investigator;
- It is the responsibility of the PI to inform the IRB of SAEs as required by the IRB procedures.

9.6 Device Deficiency Reporting Process

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the study and appropriately managed by the Sponsor.

9.7 Emergency Contact Details

IlluminOss Medical, Inc. will oversee medical monitoring for the study. In the event of an emergent event, site personnel should contact:

Fred Tobia, Vice President of Clinical, Quality, and Regulatory
IlluminOss Medical, Inc.
993 Waterman Ave.
East Providence, RI 02914
Ph: 1 (401) 714-0008 x. 231
Fax: 1 (401) 714-0009

10 Administrative Issues

10.1 Statement of Compliance

This clinical investigation will be conducted in compliance with the principles that have their origin in the Declaration of Helsinki, this clinical investigation plan, U.S. Federal regulation, the requirements of the approving Institutional Review Board, and any other applicable regulatory requirements. Any additional requirements imposed by the U.S. Food and Drug Administration will be followed, as appropriate.

10.2 Insurance

Clinical trial and liability insurance will be secured prior to investigation initiation.

10.3 Institution Review Board Opinion

The Protocol shall be reviewed and approved/given a favorable opinion by the the principal investigator's IRB prior to subject enrollment. Significant changes to the investigational plan must be approved in writing by the Sponsor, IlluminOss Medical, the IRB , prior to implementation. A significant change is one which may increase the risk or present a new risk to a subject, or which may adversely affect the scientific validity of the study.

Prior to first subject enrollment, a signed copy of the IRB's favorable opinion letter identifying the clinical study and investigational site is required to be submitted to IlluminOss Medical or the contracted renewal of the study by the IRB (according to renewal schedule imposed by the IRB). Evidence of renewal and continued IRB favorable opinion must be provided to IlluminOss Medical or the contracted CRO.

10.4 Informed Consent

If the patient meets all clinical eligibility criteria, the patient (and/or authorized legal representative) should be approached to obtain written informed consent. The background of the proposed study and the benefits and risks of the procedures and study should be explained to the patient. The patient must sign the consent form prior to any study-specific procedure or data collection. All enrolled subjects will complete the appropriate consent form that has been approved by the IRB. The consent process must be documented and copies of the signed informed consent shall be kept in the subject's medical records and study files. A copy of the informed consent form must be given to each subject (or authorized legal representative) enrolled in the study.

Modifications to the informed consent form template must have approval from IlluminOss Medical, the IRB, and FDA, as required. Subjects will be asked to sign the revised informed consent form.

10.5 Confidentiality

All information and data sent to IlluminOss Medical or their authorized representatives, concerning patients or patient participation in this study will be considered confidential. All data used in the analysis and reporting of this study will be used in a manner without identifiable reference to the subject.

10.6 Device Removal

In the event the PI deems it necessary to remove the implanted IlluminOss device, the subject will undergo the standard x-rays required in the protocol (i.e., anterior/posterior [AP], lateral, oblique) prior to and following device removal.

10.7 Device Accountability

The investigational site must keep an accurate accounting of the number of study devices received from IlluminOss Medical, dispensed to subjects, and returned to IlluminOss Medical at the end of the study. A detailed inventory must be completed including date of receipt, subject number/initials, device lot number, date of implantation, and date of return. The study device may only be dispensed by a qualified person. The study device is to be used in accordance with this protocol under the direct supervision of the PI.

10.8 Data Monitoring and Quality Control

A contracted CRO is assigned to manage the data for the investigational study on behalf of the Sponsor, IlluminOss Medical.

10.8.1 Training

The training of the PI will be the responsibility of the Sponsor, IlluminOss Medical, with the assistance of the CRO. To ensure uniform data collection and protocol compliance, the appointed monitor will perform study initiation visits to review the clinical protocol, techniques for the identification of eligible patients, instructions on in-hospital data collection, methods for soliciting data from alternative sources, and schedules for follow-up with study site personnel, and the regulatory requirements of participating in a clinical trial.

Didactic Session: The didactic session will be comprised of a presentation reviewing the concepts of the protocol and a review of any information from clinical use of the PBSS device. The team will be shown a presentation on the surgical technique and the removal technique, should the product need to be removed sometime after implantation or due to a failure of the balloon during infusion and/or curing. This session will allow all those involved in the study to pose questions regarding the investigational plan and investigational device use.

Hands-On Demonstration: In addition to the didactic segment, a practice session using modeling will allow the clinician to gain a better understanding of the system operation.

10.8.2 Case Report Forms

CRFs will be used to collect all subject data during the course of the study.

Regulatory requirements require the study subject's medical records corroborate data collected on the CRFs. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the patient before involvement in the study, sufficient to verify protocol entry criteria;
- Dated and signed notes on the day of entry into the study, including the study PI, study name, subject number assigned, and a statement that consent was obtained;
- Dated and signed notes from each study subject visit with reference to the CRFs for further

information, if appropriate (for specific results of procedures and exams);

- Information related to AEs;
- Study subject's condition upon completion of, or withdrawal from, the study;
- Discharge summaries/procedure reports.

10.8.3 Data Reporting

The PI or designated individual shall be responsible for entering all study data in the CRFs supplied by IlluminOss Medical or their authorized representative.

The PI is required to sign the CRF. All protocol deviations shall be documented and a justification for any missed assessments shall be provided on the Protocol Deviation CRF.

Completed CRFs will be verified by IlluminOss Medical and/or appointed independent monitors from the contracted CRO at the investigational site at regular intervals throughout the study. The investigator will allow the monitor and/or representative of the Sponsor, and other regulatory authorities to review and inspect the study files, subject CRFs, subject medical records, and other related study documents, as required.

10.8.4 Data Review

At routine monitoring visits, HIPAA-compliant research methods will be used to ensure that all patients presenting with impending pathological fractures secondary to metastatic bone disease were considered for participation in the study.

All CRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the monitor and will be clarified and entered by study personnel as necessary throughout the study. IlluminOss Medical or the contracted CRO may request additional documentation from the PI, such as physician procedure notes or physician written summaries, when AEs are observed and reported.

Development of the primary database for the study will be managed by IlluminOss Medical or the contracted CRO. IlluminOss Medical or the contracted CRO will also be responsible for quality control of the database and confirming the overall integrity of the data.

10.8.5 Record Maintenance

PI files containing all records and reports of the investigation should be retained for a minimum of 2 years after the completion/termination of the investigational study. They may only be discarded upon written notification by the Sponsor. To avoid error, the PI should contact IlluminOss Medical before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

In addition, in accordance with the Clinical Study Agreement, the Sponsor should be contacted if the PI plans to leave the investigational site so that appropriate arrangements for file custodianship can be made.

10.8.6 Investigational Site Monitoring

IlluminOss Medical or the contracted CRO is responsible for the monitoring of the study. The study will be monitored according to applicable provisions of CRO's clinical monitoring procedures and in compliance with regional regulations.

10.9 Clinical Investigational Protocol Amendments

No amendments to the protocol may be made without prior authorization of IlluminOss Medical Inc. and the approval of the IRB and FDA.

10.10 Deviations from Clinical Protocol and Medical Emergencies

The PI will not deviate from the clinical protocol without the prior written approval of IlluminOss Medical except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the study. In medical emergencies, prior written approval for protocol deviations will not be required, but the CRO, as the authorized representative of the Sponsor, should be notified within 24 hours of occurrence.

Deviations to the protocol will be documented on CRFs. Investigators will also adhere to procedures for reporting deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

Major deviations to the protocol may result in study termination of an investigator or investigational site.

10.11 Investigational Site Suspension or Premature Termination

If conditions arise during the study that indicate that the study or an investigational site should be terminated, the Sponsor, Investigator, Monitor, IRB, and/or regulatory agencies will discuss the situation and take appropriate action after consultation. The Sponsor reserves the right to terminate an investigational site from the study. Examples of noncompliance include, but are not limited to:

- Repeated failure to complete CRFs;
- Failure to obtain informed consent;
- Failure to report SAEs within 24 hours of knowledge;
- Loss of or unaccountable investigational device inventory;
- Repeated protocol violations;
- Failure to enroll an adequate number of subjects.

Noncompliance is defined as the Investigator not complying with an enforceable and/or agreed upon requirement. In the case of a noncompliance, corrective and preventative actions may be taken. Noncompliance also involves the Investigator not complying with or initiating an effective corrective action plan to ensure compliance. Depending on the nature of the noncompliance, the Sponsor may decide to take further action, disqualify the Investigator, terminate enrollment or terminate the site entirely.

If the study is prematurely terminated or suspended for any reason, the IRB and, if necessary, the regulatory authorities, will be informed promptly and provided with a detailed written explanation for the

termination or suspension. In the event that the study or site is terminated, all efforts will be made to ensure that all subjects will continue to be followed for the duration of their remaining time in the study.

11 Publication Policy

The conditions under which an Investigator may publish results from this clinical investigation in any form are defined in detail in the clinical study agreement.

IlluminOss Medical may at any time publish the results of, and information pertaining to, the investigational subjects only, in compliance with regulatory requirements pertaining to patient protected health information. Study results will be listed on ClinicalTrials.gov, regardless of outcome, as required by FDAAA 801, only after FDA has rendered a final decision on the marketing clearance. In the event that the study is terminated, the release of results will occur earlier.

The Sponsor, IlluminOss Medical, or their authorized agent(s) (CROs), will be responsible for notifying the health authority of the completion/termination of the investigation and shall submit a final report to the health authority and all reviewing IRBs and participating PIs after study completion/termination.

11.1 Centers for Medicare & Medicaid Services

It is expected that Medicare beneficiaries will experience the same potential risks and benefits resulting from treatment with the IlluminOss PBSS as listed in Section 4 above. Results from this investigation are expected to be generalizable to Medicare beneficiaries undergoing treatment for actual or impending pathological fractures of the humerus.

12 References

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13 Appendices

13.1 Study Definitions

A. Skeletal Definitions

New or Recurrent Fracture: Fracture of treated bone, confirmed via radiography or other imaging technique.

B. Neurologic Definitions

Stroke: neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction.

Transient Ischemic Attack (TIA): neurological deficit lasting less than 24 hours and, if an imaging study is performed, shows no evidence of infarction.

Other Neuropathy: includes events such as persistent paresthesia, and impingement of nerve roots by implants and other neurologic pathology (e.g., nerve palsy).

C. Infectious/Inflammatory Definitions

Allergic Reaction: An allergic reaction characterized by rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of-breath, vasovagal reaction, or general collapse.

Bacteremia: Presence of viable bacteria in the circulating blood. May be associated with clinical signs/symptoms such as fever. Must be confirmed by having one positive blood culture and no subsequent negative cultures.

Sepsis: one positive blood culture AND clinical evidence for infection (e.g., fever, elevated WBC count, hypotension, need for increased inotropic support, end organ dysfunction, coagulopathy/disseminated intravascular coagulation [DIC], need for increased ventilator support, etc.).

Superficial Wound Infection: confined to the dermis and subcutaneous tissue, evident by erythema, swelling, and fluctuance documented with positive culture. May require Incision and Drainage.

Deep Wound Infection: extends beneath the fascia, confirmed with positive culture, usually requiring Incision and Drainage.

Osteomyelitis: infection involving bone, confirmed by bacteriologic or histologic examination of the pathologic tissue.

Urinary Tract Infection: Documented presence of bacteria in the urine.

D. Respiratory/Pulmonary Definitions

Pneumonia: Pneumonia diagnosed by one of the following: Positive cultures of sputum, blood, pleural fluid, emphysema fluid, transtracheal fluid or transthoracic fluid; consistent with the diagnosis and clinical findings of pneumonia. Should include chest x-ray diagnostic of pulmonary infiltrates.

Pulmonary Embolism: Pulmonary embolism confirmed via pulmonary angiogram with constant intraluminal filling defect in pulmonary artery, positive CT or MRI in a high quality image study, or pathologic examination of thrombus removed at surgery or autopsy.

Respiratory Failure: New onset of respiratory insufficiency that requires placement of endotracheal tube and/or pneumothorax with or without chest tube.

E. Vascular Definitions

Acute Limb Ischemia: Any complication producing limb ischemia.

Deep Vein Thrombosis: thrombosis of a deep vein, as confirmed by imaging study or direct visualization.

Embolism (including air, fat and thromboemboli): The blockage of a blood vessel by an embolus, which can include a clot, fat globule or air bubble.

Hematoma: Clinically significant collection of blood (or serous fluid) at the operative site that requires treatment (surgical intervention, injection therapy, compression therapy) or prolongs hospitalization.

Hemorrhage: Any bleeding which results in a drop in hematocrit from pre-procedure level of greater than or equal to 6 points (2 grams of hemoglobin) or a hematocrit <30, or blood loss that requires transfusion or results in substantial hemodynamic compromise requiring treatment. Hemorrhage will be considered serious if it requires ≥ 2 units of blood or results in hemodynamic compromise.

Vascular Damage:

- Dissection: Presence of angiographically evident intimal disruption (e.g., linear luminal density or luminal staining or linear intraluminal filling defect) that requires treatment.
- Arteriovenous Fistula: A traumatic communication between an artery and vein documented by ultrasound or angiography
- Pseudoaneurysm: Compartmentalized blood contiguous with arterial lumen documented by ultrasound or visualized at repair.
- Arterial Occlusion/Thrombosis: Angiographic or ultrasonographic evidence of occlusion

F. Cardiac Definitions

Cardiac Arrhythmia: electrical event that requires specific medication, direct current (DC) shock, or pacemaker insertion to address condition.

Myocardial Infarction (new or evolving): Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

- Ischemic symptoms;
- Development of pathogenic Q waves on the ECG;
- ECG changes indicative of ischemia (ST segment elevation or depression); or
- Coronary artery intervention (e.g. coronary angioplasty)
- OR Pathogenic findings of an acute MI
- OR development of new pathogenic Q waves on serial ECGs.

Angina: A tight or heavy feeling in the chest, discomfort which spreads from the chest to the arm, back, neck, jaw, or stomach, numbness or tingling in the shoulders, arms or wrists, shortness of breath, and nausea.

Unstable Angina: Angina which increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than in stable angina, occurs at rest or with less exertion than in stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Bleeding Requiring Transfusion: Defined as any blood loss requiring transfusion of blood products.

G. Device Specific Definitions

Clinically Significant Device Migration: Change in bone pin position compared to immediate post-deployment position greater than 1cm (either proximal or distal) as documented by radiographic imaging and associated with clinical symptoms.

Device Fracture: Any loss of structural integrity (i.e. breakage or separation) of the implanted, polymerized bone pin. Documented by imaging or visually confirmed at the time of surgery or autopsy.

Subsequent Surgical Procedures:

- **Revision:** a revision is a procedure that adjusts or in any way modifies the original implant configuration. This may include adjusting the position of the original implant configuration.
- **Removal:** A removal is a procedure where the original implant is removed with or without replacement (e.g. due to mechanical failure of the implant, infection, etc.).
- **Reoperation:** a re-operation is any surgical procedure at the involved implant (or "index surgery") site that does not remove, modify or add any aspect of the implant (e.g. drainage of a hematoma at the surgical site).
- **Supplemental Fixation:** a supplemental fixation is a procedure in which additional, non-IlluminOss device(s) are implanted at the index surgical site (e.g. plates and screws). (Note: external devices such as splints or casts, which may be used in the routine care of patients with fractures, are not considered supplemental fixation).

Other Interventions: Therapeutic interventions the patient experiences during the study period, which do not meet the definition of Revision, Removal, Reoperation, or Supplemental Fixation, and are considered

unrelated to the implant, index surgical site and associated procedures and customary care of patients undergoing such procedures.

H. Other Adverse Event Definitions

Acute Renal Failure: acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of > 1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is > 2.0 mg/dl; (b) a new requirement for dialysis.

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to below 30%. Any bleeding event requiring ≥ 2 units PRBCs will be considered an SAE.

Death: all cause mortality, occurring from time of index procedure through 360 days post-index procedure.

Hypertension: Acute or severe elevation of systolic blood pressure requiring treatment.

Hypotension: Abnormally low blood pressure requiring circulatory support seen in shock but not necessarily indicative of it. It may be caused by dilation of the blood vessels, or loss of Systemic Vascular Resistance.

General Discomfort: Physical or psychosocial signs or symptoms commonly associated with hospitalization that are investigated and determined to require minor (i.e. aspirin, non-narcotic medication) or no treatment.

Nausea: The unsettling feeling in the stomach that accompanies the urge to vomit.

Pain: An unpleasant sensation occurring in varying degrees of severity as a consequence of injury, disease, or emotional disorder.

Vasovagal Reaction: Reflex stimulation of the vagus nerve resulting in slowing of the heartbeat, decreased blood pressure, etc. and requires treatment consisting of any of the following: (a) > 1 liter of IV fluids; (b) postural changes; (c) pacing intervention; or (d) administration of atropine.

Wound Dehiscence: The separation of the surgical wound after more than 24 hours of closure, which can be due to non-union, trauma, infection, or other cause.

13.2 Schedule of Activities

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening and Baseline	Surgery and Discharge	7-14 Day F/U (+3 days)	30 Day F/U (± 7 days)	90 Day F/U (± 14 days)	180 Day F/U (± 30 days)	360 Day F/U (± 30 days)
Inclusion/Exclusion Review	X						
Informed Consent	X						
Patient Medical History	X						
Physical Exam	X						
Intraoperative Data ¹		X					
Clinical Assessments ²			X	X	X	X	X
MSTS Score and EORTC QLQ BM22	X		X	X	X	X	X
Pain Visual Analog Scale (VAS)	X		X	X	X	X	X
Radiographs of Fracture Area	X		X	X	X	X	X
Adverse Events		X	X	X	X	X	X

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening and Baseline	Surgery and Discharge	7-14 Day F/U (+3 days)	30 Day F/U (± 7 days)	90 Day F/U (± 14 days)	180 Day F/U (± 30 days)	360 Day F/U (± 30 days)
Concomitant/Pain Medications	X	X	X	X	X	X	X
Health Economic Assessment	X	X	X	X	X	X	X

¹ Including date of surgery, duration of surgery, impending fracture treatment used.

² Clinical assessments: standard fracture evaluations and other assessments, as appropriate, including but not limited to assessments for pain, return to pre-treatment mobility, range of motion, return to work, disability status, use of pain medication, and physical therapy prescription status.

13.3 Post-operative Management Schema

Post-operative management will follow the standard of care for each investigator but, at a minimum, will include the follow-up visits and assessments as specified in this study protocol.