

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

July 6, 2016

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

Protocol Number: 14-03-PATHOLHUM-01

**Sponsor: IlluminOss Medical, Inc.
993 Waterman Avenue
East Providence, RI 02914
USA**

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Investigator Responsibility

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 Independent Ethics Committee (IEC). 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 IEC-approved Subject Information & Informed Consent Form (SIIC) 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 study protocol, the signed CSA, ISO 14155 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 IEC-approved form.
- Assure that the study is not commenced until IEC and Competent Authority approvals (as required) have been obtained.
- Provide all required data and agree to source document verification of study data with subject’s medical records.
- Allow staff of the Sponsor, IlluminOss Medical, Inc., and its authorized representatives, as well as representatives from the IEC and Competent Authority, to review, inspect and copy any documents pertaining to this clinical investigation.
- 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
ICF	Informed Consent Form
IFU	Instructions for Use (device)
IEC	Independent Ethics Committee
IM	Intramedullary
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MoH	Ministry of Health
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
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

Revision History

Version and Date	Changes
Version 1.0: 25 June 2014	Not applicable
Version 2.0: 6 July 2016	• Clarified actual number of enrolled subjects • Updated safety reporting information

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 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.
Study Design:	CE marking, prospective, multi-center, open label study.
Sample Size:	Up to 45 subjects are expected to be enrolled in this clinical study. Fourteen patients were enrolled.
Study Duration	Enrollment is expected to take approximately 6 months. Study subjects will be followed through the Day 90 Visit followed by the extended follow up phase out to the Day 360 Visit. The total study duration is expected to take approximately 18 months, including the enrollment period and the extended follow-up period.
Subject Population:	The investigation population consists of skeletally mature adults, suffering from pain due to single impending and actual pathological fractures of the humerus secondary to metastatic malignancy.

Inclusion Criteria:	<u>General Inclusion Criteria</u> 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. Able to understand and provide informed consent. 5. Willing and able to comply with post-operative treatment protocol and follow-up visit schedule. <u>Impending Fracture-Specific Inclusion Criteria</u> 6. Documented presence of solitary metastatic lesion. 7. Mirels Criteria Score ≥ 8. 8. Destruction of cortical bone at impending fracture site $> 50\%$. <u>Actual Fracture-Specific Inclusion Criteria</u> 9. Radiograph-confirmed diagnosis of acute, single isolated fracture of the humerus. AO classification 11A1, 11A2 and 11B1, 11B2 and 12A1,12A2 and 12B1, 12B2 and 13A1,13A2 and 13B1, 13B2. 10. Fracture is closed, Gustilo Type I or IIA.
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Exclusion Criteria:	<u>General Exclusion Criteria</u> 1. Primary tumor (osteogenic origin, etc.) at site. 2. Impending fracture or actual fracture location other than humerus. 3. Current concomitant traumatic fracture of any other location. 4. Active or incompletely treated infections that could involve the device implant site. 5. Distant foci of infection that may spread to the implant site. 6. Allergy to implant materials or dental glue. 7. Vascular insufficiency, muscular atrophy, or neuromuscular disease at implant site. 8. Uncooperative patients, or patients who are incapable of following directions (for example, as a consequence of a neurological or psychiatric disorder). <u>Impending Fracture-Specific Exclusion Criteria</u> 9. Mirels Score < 8. 10. Destruction of cortical bone at impending fracture site < 50%. 11. Prior surgery and/or prior fracture of affected site. 12. Any articular component to impending fracture site. <u>Actual Fracture-Specific Exclusion Criteria</u> 13. Index treatment is greater than 28 days post fracture. 14. Open fractures with severe contamination. 15. Extremely comminuted fractures where insufficient holding power of the balloon on the intramedullary canal is probable. 16. Delivery sheath is unable to cross fracture site after proper fracture reduction and realignment. 17. Patients whose intramedullary canal at site of fracture measures smaller than the diameter of the sheath provided.
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Primary Endpoint:	Subject success is determined by achieving the Safety and Effectiveness endpoints at the Day 90 Visit. <u>Safety Success</u> is evaluated 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 <u>Effectiveness Success</u> is evaluated by achieving Pain Reduction and Functional Improvement: • Pain Reduction ○ VAS Pain Score change of $\geq -33\%$ compared to baseline • Functional Improvement ○ Barthel Index of Activities of Daily Living (ADLs) improvement of $\geq +10\%$ from baseline ○ EORTC QLQ-C30 improvement of $> +10\%$ from baseline ○ EORTC QLQ-BM22 improvement of $> +10\%$ from baseline
Secondary Endpoints	The secondary endpoints, evaluated at the Day 90 Visits, include: 1. The seven composite endpoint components listed under the primary endpoint Other secondary endpoints include: 2. Duration of index procedure and length of hospital stay 3. Activities of Daily Living score through all follow-up intervals 4. VAS Pain score from baseline through all follow-up intervals. 5. Disability status. 6. Evaluation of duration of physical therapy prescription. 7. Assessment of prescription and over-the-counter analgesic medication use. 8. Survivability from time of index procedure to death The safety endpoints evaluated through Day 90, include: 1. Incidence and number of AEs. 2. Incidence and number of procedure and device-related complications.

	These secondary endpoints listed above will also be examined during the extended follow up portion of the trial at Day 180 and 360.
Study Sponsor:	IlluminOss Medical, Inc. 993 Waterman Avenue East Providence, RI 02914 USA Tel: 401-714-0008 Fax: 401-714-0009
Data Management	Medpace Medical Device 3787 95th Ave. NE Suite 100 Blaine, MN 55014
Core Radiographic Imaging Services	Medical Metrics, Inc. 2121 Sage Road, Suite 300 Houston, Texas 77056 Tel: (713) 850-7500 Fax: (713) 850-9996
Clinical Monitoring	Medpace Medical Device B.V. Maastrichterlaan 127-129 NL-6291 EN Vaals
Regulatory Responsibility	IlluminOss Medical, Inc. 993 Waterman Avenue East Providence, RI 02914 USA Tel: 401-714-0008 Fax: 401-714-0009
Monomer Cement Manufacturer	Dymax Corporation 318 Industrial Lane Torrington, CT 06790 Tel: 860-482-1010 Fax: 860-496-0608
Returned Goods Analysis Vendor	E ^x ponent 3401 Market Street Suite 300 Philadelphia, PA 19104 Tel: 215-594-8800 Fax: 215-594-8899

Table of Contents

Revision History	4
Protocol Synopsis.....	5
Table of Contents	10
1 Introduction	13
1.1 Impending Pathological Fractures from Cancer.....	13
1.2 Rationale for Development of the IlluminOss Photodynamic Bone Stabilization System	17
2 Intended Use & Device Description.....	18
2.1 Intended Use.....	18
2.2 Device Description	18
3 Justification for Clinical Investigation Design	19
3.1 Pre-Clinical Investigation Results	19
3.2 Prior Clinical Studies.....	19
4 Risks and Benefits	21
4.1 Anticipated Clinical Benefits	21
4.2 Anticipated Adverse Device Effects (Risks).....	21
4.3 Residual Risks Associated With the Investigational Device.....	23
4.4 Risks Associated With Participation in the Clinical Investigation.....	23
4.5 Risk Mitigation.....	23
4.6 Risk to Benefit Rationale	24
5 Study Objectives.....	24
6 Study Design	24
6.1 Study Endpoints	24
6.1.1 Primary Endpoint	24
6.1.2 Secondary Endpoints.....	25
6.2 Subject Population.....	25
6.2.1 Inclusion/Exclusion Criteria.....	25
6.2.2 Criteria and procedures for subject withdrawal or continuation	27
6.2.3 Enrollment.....	27
6.2.4 Duration of the Study	27
6.2.5 Number of Subjects	27
6.2.6 Vulnerable Population.....	28
7 Statistical Methods	28
7.1 General Methods	28

7.2	Sample Size	28
7.3	Analysis Population.....	28
7.4	Demographic and Baseline Characteristics	29
7.5	Analysis of Primary Endpoint	29
7.6	Analysis of Secondary Endpoints.....	29
7.6.1	Procedure- and Device-related Complication Rate	29
7.6.2	Duration of Index Procedure and Length of Hospital Stay	29
7.6.3	No Pain at Palpation	29
7.6.4	Pain Visual Analog Score.....	30
7.6.5	Disability Status	30
7.6.6	Range of Motion.....	30
7.6.7	Return to Work.....	30
7.6.8	Barthel Index of Activities of Daily Living	30
7.6.9	EORTC QLQ-30 and QLQ-BM22	30
7.6.10	Health Economic Analyses	30
7.6.11	Extended Follow Up Visits	30
7.6.12	Adverse Events.....	31
7.7	Optional Analyses	31
7.7.1	Fracture Location	31
7.7.2	Health Economic Data.....	31
7.8	Interim Analysis	31
8	Schedule of Subject Activities	31
8.1	Visit 1: Screening and Baseline.....	31
8.1.1	Screening.....	31
8.1.2	Baseline	31
8.2	Visit 2: Surgery and Post-index Procedures/Discharge.....	32
8.3	Follow-up Visits and Evaluations	33
8.3.1	Visit 3: 7-day Follow-up ($\pm$ 4 days)	33
8.3.2	Visit 4 and 5: 30-day Follow-up ($\pm$ 14 days) and 90-day Follow-up ($\pm$ 14 days).....	34
8.3.3	Extended Follow Up Visits 6 & 7: 180-day Follow-up ($\pm$ 30 days) and 360-day Follow-up ($\pm$ 30 days)	34
8.4	Activities Performed by Sponsor Representatives	34
9	Adverse Events, Adverse Device Effects and Device Deficiencies	34
9.1	Definitions	34
9.2	Relation to the Device and Procedure	37

9.3	Reporting to Sponsor.....	38
9.4	Reporting to Ethics Committee and Competent Authority	38
9.5	Adverse Event Reporting	38
9.6	Device Deficiency Reporting Process.....	39
9.7	Emergency Contact Details	39
10	Administrative Issues	39
10.1	Statement of Compliance	39
10.2	Insurance	39
10.3	Ethics Committee Opinion	40
10.4	Informed Consent.....	40
10.5	Confidentiality.....	40
10.6	Device Removal	40
10.7	Device Accountability.....	41
10.8	Data Monitoring and Quality Control	41
10.8.1	Training.....	41
10.8.2	Case Report Forms	41
10.8.3	Data Reporting	42
10.8.4	Data Review	42
10.8.5	Record Maintenance.....	42
10.8.6	Investigational Site Monitoring.....	43
10.9	Clinical Investigational Protocol Amendments.....	43
10.10	Deviations from Clinical Protocol and Medical Emergencies	43
10.11	Investigational Site Suspension or Premature Termination	43
11	Publication Policy.....	44
12	References	45
13	Appendices	49
13.1	Study Definitions.....	49
13.2	Schedule of Activities	53
13.3	Post-operative Management Schema	55

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. Mirels assigned these categories increasing risk scores, as the conventional belief was that the risk of fracture in weight bearing bones was greater than non-weightbearing bones.²⁰ Mirels' subsequent investigation did not confirm this assumption, and the site of lesion did not independently predict risk of fracture.¹⁹

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 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 with⁴⁸⁻⁵³ 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 Stabilization 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 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, England, 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.

The PBSS does not have CE mark clearance for the humerus yet. This study 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 pathological fracture of the humerus indication for use of the device in the European Union.

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) but not yet for the humerus. 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 still 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 147 bones have been treated in 132 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.

Bone Treated	No. Subjects Treated
metacarpal	14
fibula	20
humerus	42
humerus and femur	1
ulna	16
radius	1
distal radius	11
radius and ulna	2
distal radius and ulna	5
pelvis	4
tibia	1

Bone Treated	No. Subjects Treated
tibia and fibula	3
femur	7
sternum	1
unknown	4
TOTAL	132

Of the 132 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 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 the implantation, indwelling period, or at the time of or following device removal, if performed.

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);
- need to supplement the implant with other orthopedic devices such as screws, a plate and screws, Kirschner wires, or sutures for tuberosity fixation;
- 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 A/P, lateral and oblique radiographs taken at the Day 7, 30, 90, 180 and 360 assessments. 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 clinical study to evaluate the PBSS in the treatment of impending and actual pathological fractures of the humerus.

A total of up to 14 subjects will be recruited from up to 6 sites in the European Union.

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

Subject success is determined by achieving the Safety and Effectiveness endpoints at the Day 90 Visit.

Safety Success is evaluated 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

Effectiveness Success is evaluated by achieving Pain Reduction and Functional Improvement:

- Pain Reduction
 - VAS Pain Score change of $\geq -33\%$ compared to baseline
- Functional Improvement
 - Barthel Index of Activities of Daily Living (ADLs) improvement of $\geq +10\%$ from baseline

- EORTC QLQ-C30 improvement of $> +10\%$ from baseline
- EORTC QLQ-BM22 improvement of $> +10\%$ from baseline

6.1.2 Secondary Endpoints

The secondary endpoints, evaluated at the Day 90 Visit, and at the Extended Follow Up Visits include:

1. The seven composite endpoint components listed under the primary endpoint.

Other secondary endpoints include:

2. Duration of index procedure and length of hospital stay.
3. Activities of Daily Living score through all follow-up intervals.
4. VAS Pain score from baseline through all follow-up intervals.
5. Disability status.
6. Evaluation of duration of physical therapy prescription.
7. Assessment of prescription and over-the-counter analgesic medication use.
8. Survivability from time of index procedure to death.

The safety endpoints evaluated include:

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

6.2 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.

6.2.1 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. Able to understand and provide informed consent.
5. Willing and able to comply with post-operative treatment protocol and follow-up visit schedule.

Impending Fracture-Specific Inclusion Criteria

6. Documented presence of solitary metastatic lesion.
7. Mirels Criteria Score ≥ 8 .
8. Destruction of cortical bone at impending fracture site $> 50\%$.

Actual Fracture-Specific Inclusion Criteria

9. Radiograph-confirmed diagnosis of acute, single isolated fracture of the humerus. AO classification 11A1, 11A2 and 11B1, 11B2 and 12A1, 12A2 and 12B1, 12B2 and 13A1, 13A2 and 13B1, 13B2.
10. Fracture is closed, Gustilo Type I or IIA.

General Exclusion Criteria

1. Primary tumor (osteogenic origin, etc.) at site.
2. Impending fracture or actual fracture location other than humerus.
3. Current concomitant traumatic fracture of any other location.
4. Active or incompletely treated infections that could involve the device implant site.
5. Distant foci of infection that may spread to the implant site.
6. Allergy to implant materials or dental glue.
7. Vascular insufficiency, muscular atrophy, or neuromuscular disease at implant site.
8. Uncooperative patients, or patients who are incapable of following directions (for example, as a consequence of a neurological or psychiatric disorder).

Impending Fracture-Specific Exclusion Criteria

9. Mirels Score < 8 .
10. Destruction of cortical bone at impending fracture site $< 50\%$.
11. Prior surgery and/or prior fracture of affected site.
12. Any articular component to impending fracture site.

Actual Fracture-Specific Exclusion Criteria

13. Index treatment is greater than 28 days post fracture.
14. Open fractures with severe contamination.
15. Extremely comminuted fractures where insufficient holding power of the balloon on the intramedullary canal is probable.
16. Delivery sheath is unable to cross fracture site after proper fracture reduction and realignment.
17. Patients whose intramedullary canal at site of fracture measures smaller than the diameter of the sheath provided.

6.2.2 Criteria and procedures for subject withdrawal or continuation

6.2.2.1 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.

6.2.2.2 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.

6.2.2.3 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.

6.2.3 Enrollment

The study will be described to skeletally mature adult males and females presenting with a single painful impending and 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 providing informed consent. Patients who fail one or more of the eligibility criteria are considered screening/enrollment failures and are exited from the study.

6.2.4 Duration of the Study

The enrollment period is expected to be approximately 6 months. Subjects will be followed for 90 days after treatment and then followed in an extended follow up phase for up to 360 days. The total duration of the clinical investigation is thus expected to be approximately 18 months.

6.2.5 Number of Subjects

An estimated 45 subjects were planned to be enrolled in the study with a goal of enrolling 30 subjects who meet eligibility criteria and are not lost-to-follow-up. No minimum or maximum number of subjects

per participating center has been set. The study was discontinued after the 14th patient was enrolled due to slow enrollment and a higher than expected drop out rate resulting from progression of metastatic disease. Forty-nine patients from a similar study conducted in the United States will be used to supplement the data from this study.

6.2.6 Vulnerable Population

The subject population of this clinical investigation does not meet the criteria for a vulnerable population as defined in ISO 14155, Section 3.44. If a subject loses ability to consent during the course of the study this will lead to study exit. Such subjects will be followed on safety parameters for the course of the study, but their data will not be used for data analysis.

7 Statistical Methods

7.1 General Methods

The planned methods for the final data analysis will be detailed in the Statistical Analysis Plan (SAP), which will be written and approved prior to locking the database.

Statistical analyses will be descriptive only, including 95% confidence intervals, with no hypothesis testing. All study data will be presented in by-subject data listings.

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

Sample size for this clinical investigation was not statistically determined. The Sponsor decided that 30 subjects need to be enrolled and followed through 3 months to adequately describe the ability to implant the IlluminOss Photodynamic Bone Stabilization System and describe the safety and performance of the IlluminOss Photodynamic Bone Stabilization System in this patient population. An extended follow up period of 360 days after implantation surgery is included in the protocol to include long term follow up on this patient population. Due to potential enrollment failures, loss-to-follow-up and survival secondary to metastatic disease, it was decided that 45 subjects will be sufficient to ensure that at least 30 subjects are followed through 3 months. With the US data available, there will be 30 patients with 90 day data presented.

7.3 Analysis Population

The Intent-to-Treat (ITT) analysis population is defined as all subjects who meet the study eligibility criteria, provide informed consent, undergo surgery, and have a successful implantation of the IlluminOss Photodynamic Bone Stabilization System into the intramedullary canal.

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.

7.5 Analysis of Primary Endpoint

The proportion of subjects who are confirmed to be a subject success at the Day 90 visit will be presented, along with the corresponding 95% binomial confidence intervals. If the proportion of subjects considered a subject success at the Day 90 Visit is at least 80% then the primary endpoint will be met.

Subject success is determined by achieving the Safety and Effectiveness endpoints at the Day 90 Visit.

Safety Success is evaluated 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

Effectiveness Success is evaluated by achieving Pain Reduction and Functional Improvement.

- Pain Reduction
 - VAS Pain Score change of $\geq -33\%$ compared to baseline
- Functional Improvement
 - Barthel Index of Activities of Daily Living (ADLs) improvement of $\geq +10\%$
 - EORTC QLQ-C30 improvement of $> +10\%$ from baseline
 - EORTC QLQ-BM22 improvement of $> +10\%$ from baseline

7.6 Analysis of Secondary Endpoints

7.6.1 Procedure- and Device-related Complication Rate

The proportion 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.

7.6.2 Duration of Index Procedure and Length of Hospital Stay

Descriptive statistics for duration of index procedure and length of hospital stay will be presented.

7.6.3 No Pain at Palpation

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

7.6.4 Pain Visual Analog Score

Summary statistics of pain VAS scores will be presented at baseline and each follow-up visit. Additionally, change from baseline will be presented at each follow-up visit.

7.6.5 Disability Status

The number and percentage of subjects who are considered disabled, per Investigator assessment, will be presented at each follow-up visit.

7.6.6 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.

7.6.7 Return to Work

The number and percentage 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.

7.6.8 Barthel Index of Activities of Daily Living

The Barthel ADL Index is an ordinal scale used to measure performance in activities of daily living. Each performance item is rated on this scale with a given number of points assigned to each ranking, using ten variables describing ADL and mobility. A higher number is associated with a greater likelihood of being able to live at home independently.

7.6.9 EORTC QLQ-30 and QLQ-BM22

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients; the QLQ-BM22 survey is specific to patients with bone metastases (BM). Both instruments were developed by the European Organization for Research and Treatment of Cancer.

7.6.10 Health Economic Analyses

If available, 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 p-values will be presented.

7.6.11 Extended Follow Up Visits

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

7.6.12 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.

7.7 Optional Analyses

7.7.1 Fracture Location

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).

7.7.2 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.

7.8 Interim Analysis

No interim analysis will be done.

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;
- Patient-completed Barthel Index Score, EORTC QLQ-C30 and QLQ-BM22
- 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 is considered a treatment failure and does not participate further in the study.

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, 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-day Follow-up (± 4 days)

The following will be performed:

- AE assessment;
- Concomitant/pain medications;
- Subject-completed pain VAS; and
- Barthel Index Assessment; EORTC QLQ-C30 and QLQ-BM22
- Clinical assessments that include, but are not limited to, assessments for pain, return to baseline mobility, return to work, disability status, use of pain medication, and physical therapy prescription status;
- Radiographs of treatment site.

If available, additional health economic data may be obtained.

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

The following will be performed:

- AE assessment;
- Concomitant/pain medications;
- Subject-completed pain VAS;
- Barthel Index Assessment; EORTC QLQ-C30 and QLQ-BM22
- Clinical assessments that include, but are not limited to, assessments for pain, return to baseline mobility, return to work, disability status, use of pain medication and physical therapy prescription status;
- Radiographs of treatment site (standard of care at 30-day follow-up visit).

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;
- Barthel Index Assessment; EORTC QLQ-C30 and QLQ-BM22
- Clinical assessments that include, but are not limited to, assessments for pain, return to baseline mobility, return to work, disability status, use of pain medication and physical therapy prescription status;
- Radiographs of treatment site.

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.

NOTE 1: This includes events related to the procedures involved (any procedure in the clinical investigation plan).

NOTE 2: For users or other persons this is restricted to events related to the investigational medical device.

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.

Adverse Device Effect (ADE): AE related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect (SADE): ADE that has resulted in any of the consequences characteristic of an SAE.

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.

Unanticipated Serious Adverse Device Effect (USADE): an AE is considered to be a USADE if there is an occurrence of a serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, the device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or if any other unanticipated serious problem associated with the device occurs, which 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.

Concomitant Medication-related AE: an AE is considered to be concomitant medication-related when, in the judgment of the PI, it is reasonable to believe that the event is associated with concomitant medications used in conjunction with the investigational device and is not otherwise specific to the investigational device (e.g. bleeding associated with anticoagulation medication).

Pre-existing Condition-related AE: an AE is considered to be related to a pre-existing condition when, in the judgment of the PI, it is reasonable to believe that the event is associated with the patient's pre-existing condition and is not specific to the investigational device or procedure. Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to determine if they may be more appropriately classified as device related or procedure related.

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 wrist 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, SAEs, UADEs, and/or unanticipated USADEs shall be reported by the PI (or designee) to the study Sponsor or CRO via telephone +31 43 3063320, email (safety.mmd@medpace.com) or facsimile +31 43 3063338 within 24 hours of learning of the AE.

The PI (or designee) shall send a written report, including a narrative description of the SAE/SADE/USADE/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 Ethics Committee and Competent Authority

All SAEs (including deaths), USADEs, SAEs, and/or UADEs shall be reported to the IEC and regulatory authority, 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
- any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate
- new findings/updates (e.g. outcome) in relation to already reported events

All reportable events must be reported to all national competent authorities where the clinical investigation has commenced, in accordance with the local requirements.

In Germany, all serious adverse events reporting to the competent authority will be reported immediately without justified delay by both the sponsor (or its representative contracted CRO) and the investigator according to §3 (5) of the Ordinance on Medical Devices Vigilance (MPSV).

The Sponsor (or its representative) shall ensure that SAEs are reported to the Ethics Committees 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, concomitant medications, pre-existing condition, 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 IEC of SAEs as required by the IEC 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

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

Medpace Medical Device Safety
Email: safety.mmd@medpace.com
Phone: +31.43.306.3320
Fax: +31.43.306.3338

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, the requirements of the approving IEC, ISO 14155, and other applicable regulatory requirements. Any additional requirements imposed by an IEC or regulatory authority will be followed, as appropriate.

10.2 Insurance

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

10.3 Ethics Committee Opinion

The Protocol shall be reviewed and approved/given a favorable opinion by the local health authority and the principal investigator's EC prior to subject enrollment. Significant changes to the investigational plan must be approved in writing by the Sponsor, IlluminOss Medical, the EC, and the local health authority 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 EC's favorable opinion letter identifying the clinical study and investigational site is required to be submitted to IlluminOss Medical or the contracted CRO, signifying study approval. Principal Investigators are responsible for obtaining and maintaining annual renewal of the study by the EC (or according to renewal schedule imposed by the EC). Evidence of renewal and continued EC 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. Failure to obtain signed informed consent renders the patient ineligible for the study. All enrolled subjects will complete the appropriate consent form that has been approved by the local health authority and the EC. 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 EC, and the local health authority, as required. Subjects may 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.

All requirements for device return and evaluation are documented in a device retrieval kit provided by the Sponsor.

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.

ISO 14155 Guidelines require that PIs maintain information in the study subject's medical records that 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 Ethics committee and Competent Authority.

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 IEC in accordance with their specific IEC 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, IEC, 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 IEC 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.

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 IECs and participating PIs after study completion/termination.

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13 Appendices

13.1 Study Definitions

A. Skeletal Definitions

Delayed Union: defined as fracture not healing as quickly as anticipated; i.e. absence of trabecular bridging bone across the fracture site(s) based on radiographic views at 180 days post-index procedure.

Malunion: a fracture for which the bone did not achieve anatomical alignment upon healing; often evidenced by patient report of pain on palpation and/or manipulation.

Pseudoarthrosis (non-union): failure to achieve fusion at the involved fracture site based upon radiographic and clinical criteria by 360 days (12 months) post-index procedure.

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 Day F/U (± 4 days)	30 Day F/U (± 14 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		X	X	X	X	X
Intraoperative Data ¹		X					
Clinical Assessments ²		X	X	X	X	X	X
Barthel Index of ADLs; EORTC QLQ-C30 & QLQ-BM22	X		X	X	X	X	X
Pain Visual Analog Scale (VAS)	X		X	X	X	X	X
Radiographs of Fracture	X		X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Concomitant/Pain Medications	X	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 Day F/U (± 4 days)	30 Day F/U (± 14 days)	90 Day F/U (± 14 days)	180 Day F/U (± 30 days)	360 Day F/U (± 30 days)
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, 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.