

CE Marking Study of the IlluminOss
Photodynamic Bone Stabilization System for
the Treatment of Humerus Fractures

NCT02394080

Study Protocol

December 9, 2015

CE Marking Study of the IlluminOss[®] Photodynamic Bone Stabilization System for the Treatment of Humerus Fractures

Protocol Number: 12-03-EUHUM-01

**Sponsor: IlluminOss Medical, Inc.
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East Providence, RI 02914
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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 Ethics Committee (EC). This approval must be in the PI’s name and a copy sent to the Sponsor, IlluminOss Medical, Inc. or their representative along with the EC approved Informed Consent Form (ICF) and the signed Clinical Study Agreement (CSA), prior to first clinical use of the investigational device.

The PI must also:

- Conduct the study in accordance with the study protocol, the signed CSA, Good Clinical Practices, the Declaration of Helsinki, and all applicable national/local regulations.
- Agree to participate in an appropriate training program prior to study initiation.
- Assure that informed consent is obtained from each subject prior to enrollment, using the EC approved form.
- Assure that the study is not commenced until EC and Competent Authority (CA)/Ministry of Health (MoH) approval (as required) have been obtained.
- Provide all required data and agree to source document verification of study data with patient’s medical records.
- Allow staff of the Sponsor, IlluminOss Medical, Inc., and its authorized representatives, as well as representatives from the CA/MoH, to review, inspect and copy any documents pertaining to this clinical investigation.
- Complete all case report forms 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 patient 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

Abbreviations

Abbreviation	Meaning
AE	Adverse Event
AP	Anterior/posterior
CA	Competent Authority
CE	Conformité Européene
CRO	Contract Research Organization
CSA	Clinical Study Agreement
EC	Ethics Committee
PBSS	IlluminOss Photodynamic Bone Stabilization System
ICF	Informed Consent Form
IFU	Instructions for Use (device)
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MoH	Ministry of Health
PI	Principal Investigator
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SOC	System Organ Class
TAM	Total Active Motion
TEAEs	Treatment-Emergent Adverse Events
TPM	Total Passive Motion

USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

Revision History

Version and date	Changes
Version 1.0 (30 July 2012)	First version
Version 1.1 (21 September 2012)	• Exclusion criteria 4 and 10 were clarified • Exclusion criterion 9 (probable history of infection) was deleted • Section 7.11: it is further explained if and when Visits 1 and 2 may occur on the same day.
Version 1.2 (13 November 2012)	• Inclusion criterion 3 (18 years revised to 61 years) • Inclusion criterion 5 (to exclude legally incompetent patients)
Version 1.3 (15 November 2012)	• Inclusion criterion 4 was removed (pregnancy test not required for patients >61 years old) • Pregnancy testing was removed from baseline visit in section 7.10.2
Version 1.4 (22 November 2012)	• SAE definition and reporting procedure matched to definitions of the MPSV • Added contact details of responsible person for monitoring and reporting of SAEs.
Version 1.5 (06 March 2013)	• Added AO classifications to the fracture specific inclusion criteria.

Version 2.0 (17 September 2014)	• Study entry criteria were amended to increase age range, allow for increased number of days for index treatment post-fracture, and establish entry criteria for women of child-bearing potential due to the increase in age range. EU Registry information also updated.
Version 3.0 (21 September 2015)	• Clarified AO Classification entry criteria • Changed the Disability of the Arm, Hand and Shoulder and Constant shoulder scores to optional assessments. • Changed designated Contract Research Organization from Factory-CRO and PROMETRIKA to Medpace Medical Device B.V. • Updated safety reporting information.

Protocol Synopsis

Title: CE Marking Study of the IlluminOss Photodynamic Bone Stabilization System for the Treatment of Humerus Fractures

Device: IlluminOss Photodynamic Bone Stabilization System (PBSS)

Study Objective: The purpose of the study is to collect safety and performance data on the use of the PBSS when used to provide stabilization and alignment for the treatment of acute humerus fractures.

Study Design: CE marking, prospective, multi-center, open label study.

Sample Size: Up to 45 patients are expected to be enrolled in this clinical study.

Study Duration Study subjects will be followed through the Day 360 Visit. The duration of the study, from first patient enrolled until last patient last visit and database lock, is estimated to be 24 months.

Patient Population: The investigation population consists of skeletally mature subjects with acute, single, isolated humerus fractures.

Inclusion Criteria: Fracture-Specific Inclusion Criteria

1. Radiograph-confirmed diagnosis of acute, single isolated fracture of the humerus. AO classification 11A2, 11A3 and 11B1, 11B2 and 12A1, 12A2, 12A3 and 12B1, 12B2.
2. Fracture is closed, Gustilo Type I or II.

General Inclusion Criteria

3. Skeletally mature men and women, 50 years of age or older at time of index injury.
4. a) Female patients of child bearing potential agree to use double barrier method of contraception
b) Female patients of non-child bearing potential must meet one of the following criteria:
 - Postmenopausal for at least 1 year, or
 - Documented oophorectomy or hysterectomy, or
 - Surgically sterile
5. Willing and able to understand and sign the informed consent.

**Exclusion
Criteria:**

Fracture-Specific Exclusion Criteria

1. Index treatment is greater than 28 days post fracture
2. Open fractures with severe contamination.
3. Extremely comminuted fractures where insufficient holding power of the balloon on the intramedullary canal is probable.
4. Marked bone loss or bone resorption patients, who due to a prior delayed union or non-union of the bones or other illnesses, may not be able to have their fracture adequately reduced prior to placement of the IlluminOss-device. This could leave bone void spaces that would preclude the device from maintaining alignment of the fractured bone.
5. Previous fracture of affected limb.

General Exclusion Criteria

6. Pregnant or lactating.
7. Active or incompletely treated infections that could involve the site where the device will be implanted.
8. Distant foci of infections that may spread to the implant site
9. Uncooperative patients or patients, who are incapable of following directions (for example as a consequence of a neurological or psychiatric disorder).
10. Concomitant metabolic disorders that may impair bone formation.
11. Osteomalacia.
12. Allergic to implant materials or dental glue.
13. Vascular insufficiency, muscular atrophy, or neuro-muscular disease.
14. Polytrauma patients (multiple injuries resulting from a high impact event, eg- a motor vehicle accident).
15. Life expectancy less than one year due to concurrent illness.

Primary Endpoint: The primary endpoint is the assessment of normal radiographic fracture healing; determined at the Day 180 visit. Normal radiographic healing is defined by two of four cortices or two of four views demonstrating bridging on standard radiographs.

Secondary Endpoints The secondary endpoints, evaluated at Day 180 and Day 360, include:

1. Assessment of the incidence of adverse events.
2. Assessment of the procedure- and device-related complication rate.

The performance secondary endpoints include:

1. Evaluation of complete radiographic healing at Day 180, defined as three of four cortices or three of four views demonstrating bridging, with dissolution of the majority ($\geq 75\%$ on orthogonal views) of fracture lines.
2. Evaluation of normal radiographic healing at Day 360.
3. Evaluation of complete radiographic healing at Day 360, defined as three of four cortices or three of four views demonstrating bridging, with dissolution of the majority ($\geq 75\%$ on orthogonal views) of fracture lines.
4. Assessment of no pain at palpation status.
5. Assessment of return to pre-fracture mobility status.
6. Comparison of pain visual analog score (VAS) from baseline to all follow up intervals.
7. Comparison of Disability of the Arm, Shoulder and Hand score from baseline to all follow up intervals.
8. Comparison of Constant shoulder score from baseline to all follow up intervals.
9. Assessment of range of motion.
10. Assessment of disability status.
11. Assessment of return to work status.

**Optional
Assessments**

In addition to disability and return to work status, the following health economic data will be analyzed:

1. Evaluation of duration of physical therapy prescription.
2. Assessment of the use of supportive orthopedic devices post-surgery.
3. Assessment of prescription and over-the-counter analgesic medication use.

**Europe
Contract
Research
Organization:
Clinical
Monitoring
and Safety
Reporting**

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1 Introduction

1.1 Fractures of the Humerus

Proximal humerus fracture is the second most common fracture of the upper extremity accounting for 5% of all fractures, and in the age group of 65 years or older, proximal humerus fractures accounts for 10% of all fractures.¹ Fractures of the humeral shaft are also commonly found, accounting for approximately 3% of all fractures.²⁰ Distal and diaphyseal humerus fractures are less common than proximal fractures, diaphyseal fractures accounting for about 20%⁹ of all humeral fractures. The treatment objective in all humerus fractures is to facilitate healing of the bone and soft-tissue in order to maximize function of the upper extremity while minimizing risk to the patient.

The ultimate goal of treating a humerus fracture is to restore full arm function as early as possible. Full range of motion in the shoulder declines with disuse and the introduction of early motion following a fracture injury is critical for the early restoration of normal function. Fracture stabilization is important in the treatment technique, as it allows for early range of motion while minimizing additional short term injury.^{1, 2} Due to the location of the humerus bone, casting is not a possible form of treatment for most serious types of humerus fractures. Fractures close to the shoulder and elbow joints, and fractures where bone fragments that are far out of position are likely to require intervention.⁹ When needed, operative intervention to reduce and stabilize humerus fracture involves either the use of a plate fixation system or the use of an intramedullary rod with pin or screw fixation. While effective in fracture reduction, current technologies are associated with significant complications related to the surgical procedures, and the procedure may impact the ability of the patient to regain early movement of their fractured limb.

Plate Fixation

Plate fixation is indicated in situations where anatomic reduction and stabilization cannot be maintained with simpler, less invasive techniques. These include fractures with segmental bone loss, and open fractures where early range of motion is desirable due to a substantial amount of swelling and soft tissue trauma.^{16, 17} Advantages of plate fixation include a reduced incidence of nonunion and greater strength of fracture fixation immediately after the reduction, enabling an early return to motion. Although plate and screw fixation afford excellent stability, plating is very time consuming and requires a greater amount of soft tissue dissection from the bone. Despite conceptual advantages offered by stable, open reduction in providing precise alignment

and stability, plate fixation involves an invasive open surgical technique, with increased complications and soft tissue damage. Research has demonstrated that a number of complications are associated with plate and screw fixation²⁰, including pain, plate prominence, infection and tendon adhesions, and a higher incidence of symptomatic fibrous unions or nonunions.^{2,11} Furthermore, plates are usually removed after the fracture has healed, requiring a second surgical procedure.

Even with newer plating, research has reported complications rates up to 35%.^{2,21} A recent prospective, multi-center observational post-marketing study of a locking proximal humerus plate reported an overall complication rate of 34%. Over half of the complications were directly related to the surgical procedure itself, and included primary screw perforation, plate impingement and neurological lesions. In addition, 19% of the patients required a second operation within the first twelve months post-treatment, and 10% of the patients had their implants removed.

Intramedullary Nail Devices

Intramedullary (IM) nailing has certain advantages over plates and screws. The IM nail is closer to the normal mechanical axis and can act as a load-sharing device if there is cortical contact. The nails are subjected to lower bending forces, making failure by fatigue less likely.⁶

Percutaneous intramedullary fixation may be an ideal way to stabilize proximal and distal articular extension fractures.¹⁰ Research has described the importance of introducing early motion following fracture, in order to allow for the restoration of normal function. Intramedullary fixation is an important technique as it provides stability and enables range of motion.¹ It may be particularly important in the treatment of proximal and distal intra-articular extension of a diaphyseal humeral fractures, which are rarely stable and routinely require internal fixation with pins or screws to maintain alignment.⁴ Current devices are associated with and overall complication rate of 35%, based on a review of literature.^{7,14,17,20} Complications associated with the use of intramedullary nail systems include delayed union, device displacement, and nerve impingement. Overall, insertion site morbidity remains a concern, and a meticulous technique is required for surgical success.⁶

1.2 Rationale for Development of the IlluminOss Photodynamic Bone Stabilization System (PBSS)

According to the Arbeitsgemeinschaft für Osteosynthesefragen/Association for the Study of Internal Fixation (AO) Foundation, the four principles for internal fixation are: 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.¹⁹ The above principles guided the development of the IlluminOss Photodynamic Bone Stabilization System.

The IlluminOss Photodynamic Bone Stabilization System (PBSS) may be uniquely suited to meeting the needs of fracture fixation, by providing longitudinal stability along the length of the device. A small, percutaneous incision is required to insert the device, with minimal soft tissue and nerve stripping. The use of the PBSS has been associated with shorter operative times when used in CE-marked applications, preserving blood and nerve pathways intra- and post-operatively. As of June 2011, no procedural or intra-operative adverse device events have been reported when the device has been used to treat fractures per CE label indications.

The non-compliant balloon spans the fracture, and conforms to the patient's unique intramedullary canal, providing stable internal fixation. After the bone pin has been hardened with the application of a visible light, additional hardware (pins and screws) may be used to stabilize the fracture. The location of the pins and screws is not pre-determined by the device, as is the case with other commercially available IM bone pins. This allows the surgeon to provide an optimum environment for normal biological healing to occur, preserving the blood supply to the bone. Obstructive bracing is not required after implantation, and only a small surgical dressing is used to treat the entry incision. Therefore, the patient is able to move the affected area immediately after surgery and may begin returning to his or her baseline level of activity.

2 Device Description & Intended Use

2.1 Intended Use

The IlluminOss PBSS is indicated for use in fracture alignment reduction. It received CE Mark clearance in 2009 for use in the treatment of phalange, metacarpal, distal radius, radius, ulna, olecranon, clavicle and fibula fractures. It provides stabilization for bone fractures using a minimally invasive technique in which the bone is not subjected to significant weight bearing forces. As of June 2012, the PBSS has been used to treat over 71 bones in 65 patients in Chile, England, Germany and Hungary. More information regarding device use is provided in Section 3 of the protocol.

This pre-market study will evaluate the use of the PBSS in the treatment of acute humerus fractures, and the results of this study will be used to support expanding the intended use of the system.

The device is manufactured by IlluminOss Medical, Inc. The monomer is manufactured by Dymax Corporation. The PBSS is comprised of an inflatable, thin walled polyethylene terephthalate (PET; Dacron) balloon mounted on an insertion catheter. It is designed to deliver the balloon system to the fracture site via the medullary canal of the bone.

Once the balloon is in place and has spanned the fracture site, the delivery sheath is removed, uncovering the balloon; the balloon is then infused with a light curable monomer via a syringe,

causing the balloon to expand. The inflated balloon fills the medullary canal on both sides of the fracture, thereby applying a transverse reduction force to the fracture.

The bone is visualized under fluoroscopy to ensure that the fracture has been properly reduced, with the balloon in the appropriate position, fully inflated and contacting the inner diameter of the bone.

The light system is activated, causing the photo initiator in the monomer to rapidly polymerize and harden in situ. The cured balloon 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 underwent biocompatibility testing that included genotoxicity, cytotoxicity, systemic sub-acute and sub chronic toxicity, sensitivity and irritation testing, and implant performance evaluations. They were tested under conditions of standard use and under failure mode conditions to assess the safety and performance of the implant materials in pre-clinical models. The tests were conducted under GLP conditions by an independent laboratory. The results of the panel of testing indicated that the presence of either the uncured monomer or the cured polymeric bone pin was well-tolerated in animal models, had no negative effect on cell viability, and is 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. The testing evaluated all mechanical, electrical, software and user-interface functionalities in compliance with international standard IEC 60601-1, 2nd and 3rd edition. The testing was conducted by an independent, certified testing agency. A standard, commercially available 75 watt light bulb is used within the unit that transmits light into the lumen of the catheter through a plastic light fiber. The safety and performance of the light outputs (wavelength and intensity spectrum) have passed all testing conducted by a second independent, certified testing agency.

3.2 Prior Clinical Results

As indicated earlier in the protocol, the PBSS has been cleared for use in the European Union (EU). The continued success of these earlier indications is the rationale for performing this investigational study of the PBSS in the humerus.

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 three subjects from November 2008 until August 2009. Due to business reasons, enrollment into the study closed in 2009. The subjects met 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 the visits, subjects were assessed for adverse device effects, clinical healing, alignment, the subjects completed a Disability of the Arm, Shoulder and Hand (DASH) questionnaire and radiographs were obtained. The Principal Investigator reported that all subjects were clinically healed by the Day 45 Visit, and no local or systemic device-related complications were reported.

EU Registry Study

The EU Registry for the IlluminOss Photodynamic 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 outcome data on treated patients. The subjects may be followed either until they are discharged from clinical care, or will be followed for up to two years post index surgery. Standard-of-care information is collected, and radiographs of the fracture site may be obtained at the discretion of the surgeon. Enrollment closed in January 2014. A total of 131 subjects have enrolled into the registry. No local or system adverse device effects have been reported. The device has also been used with additional hardware (plates and screws or screws alone).

Bone Treated	No. Subjects Treated
metacarpal	14
fibula	20
humerus	42
humerus and femur	1
ulna	15
radius	1
distal radius	12
radius and ulna	2

Bone Treated	No. Subjects Treated
distal radius and ulna	5
pelvis	4
tibia	1
tibia and fibula	3
femur	7
sternum	1
unknown	3
TOTAL	131

4 Risks and Benefits

4.1 Anticipated Clinical Benefits

Patients may benefit from participating in the study by having a shorter operative time to treat their fracture, having a shorter length of hospital stay, by requiring fewer narcotic and physical therapy prescriptions, having fewer overall complications, and by regaining the use of their affected arm sooner than if they were treated with conventional humerus plates or IM rods. Patients may not experience benefits. The results of the study will benefit the medical community treating humerus fractures by evaluating the safety and performance of the PBSS.

4.2 Anticipated Adverse Device Effects

Adverse events that may be anticipated in this clinical study are believed to be similar to and consistent with those associated with upper arm fractures, anesthesia, and surgical treatment, including the use of other commercially available 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 system or rod, possible risks may include, but are not limited to, the following:

- loosening, bending, cracking of the components or loss of fixation in bone attributable to delayed union, non-union insufficient quality or

quantity of bone

- loss of anatomic position with nonunion or malunion with rotation or angulation

In addition, there is a rare chance that the balloon catheter may become damaged and leak the chemical into the space of the fractured bone prior to the application of the light source to harden the bone pin. No local or systemic effects were observed when uncured monomer was placed either in the intramedullary canal or in the abdominal cavity during pre-clinical animal studies.

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

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

- Infection;
- False joint formation;
- Joint stiffness or inability to stretch out the arm, elbow, wrist, or fingers;
- Permanent numbness or weakness in the arm;
- Fractured bones do not heal together properly, or may heal with a bent shape;
- 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 side effects or complications of the use of anesthesia that are much more rare 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 humerus fracture reduction surgery. Enrolled patients will have Neutral Grashey, Axillary and Scapular Y radiographs taken during specified follow-up assessments. These radiographs are considered standard of care in most hospital systems. In the event that these are not considered standard of care at any given timepoint, the risk of exposure to extra radiation is expected to be less than the level of exposure during an airplane flight.

4.5 Risk Mitigation

Risks will be minimized by ensuring that only trained surgeons participate as investigators in the study. Strict patient inclusion and exclusion criteria will be followed, enrolling only patients who meet criteria and sign informed consent. During all follow up visits, patients will be assessed for any adverse events, with particular attention to events that may be related to the surgical procedure or investigational device. Medical monitoring will be conducted to review the frequency, severity, and relatedness of adverse events. In addition, the study will be monitored to ensure the compliance with the protocol and to ensure the continued acceptability of the investigator and institution.

4.6 Risk to Benefit Rationale

The potential benefits to the enrolled subjects and the medical community outweigh the potential risks identified in the protocol. The robust preclinical testing has demonstrated the safety of the

device components and all materials that may 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. The study has been designed to provide frequent safety assessments to identify any potential newly identified risks.

5 Study Objectives

The primary objective of the study is to collect safety and performance data on the use of the PBSS when used to provide stabilization and alignment for the treatment of acute humerus fractures.

6 Study Design

This is a CE marking, prospective, multi-center, open-label clinical study with the purpose of assessing performance of the PBSS in the treatment of acute fractures of the humerus.

A maximum of 45 patients undergoing IlluminOss device implant are expected to be enrolled in the study. Each patient enrolled in the study will be followed to 1 year post-index procedure.

Subjects in whom IlluminOss Photodynamic Bone Stabilization System placement is attempted but not achieved are considered enrollment failures and will not be included in the study. The reasons for unsuccessful implantation will be recorded.

6.1 Study Endpoints

The following study endpoints will be evaluated in all patients in whom the IlluminOss Photodynamic Bone Stabilization System is successfully placed. All endpoints are patient-based unless otherwise specified.

6.1.1 Primary Endpoint

The primary endpoint is the assessment of normal radiographic fracture healing; determined at the Day 180 visit. Normal radiographic healing is defined by 2 of 4 cortices or 2 of 4 views demonstrating bridging on standard radiographs.

6.1.2 Secondary Endpoints

The secondary endpoints for this study include the following assessments:

1. Incidence of adverse events at Day 180 and Day 360.
2. Procedure- and device-related complication rate at Day 180 and Day 360.

3. Complete radiographic healing at Day 180. Complete radiographic healing is defined as 3 of 4 cortices or 3 of 4 views demonstrating bridging, with dissolution of the majority ($\geq 75\%$ on orthogonal views) of fracture lines.
4. Normal radiographic healing at Day 360.
5. Complete radiographic healing at Day 360, defined as 3 of 4 cortices or 3 of 4 views demonstrating bridging, with dissolution of the majority ($\geq 75\%$ on orthogonal views) of fracture lines.
6. Identification of duration of index procedure and length of hospital stay.
7. No pain at palpation status.
8. Return to pre-fracture mobility status.
9. Comparison of pain visual analog score (VAS) from baseline to all follow up intervals.
10. Comparison of Disability of the Arm, Shoulder and Hand (DASH) score from baseline to all follow up intervals.
11. Comparison of Constant shoulder score from baseline to all follow up intervals.
12. Range of motion.
13. Disability status.
14. Return to work status.

6.1.3 Optional Assessments

The primary and secondary endpoints may be analyzed by fracture location.

In addition to disability and return to work status, the following health economic data may be analyzed:

- a) Duration of physical therapy prescription.
- b) The use of supportive orthopedic devices post-surgery.
- c) The use of prescription and over-the-counter analgesic medication.

6.2 Subjects

The investigation population will include skeletally mature adult subjects with a single, acute, isolated humerus fracture. Subjects meeting the following eligibility criteria will be included.

6.2.1 Inclusion Criteria

Fracture-Specific Inclusion Criteria

1. Radiograph-confirmed diagnosis of acute, single isolated fracture of the humerus. AO classification 11A2, 11A3 and 11B1, 11B2 and 12A1, 12A2, 12A3 and 12B1, 12B2.
2. Fracture is closed, Gustilo Type I or II.

General Inclusion Criteria

3. Skeletally mature men and women, 50 years of age or older at time of index injury.
4. a) Female patients of child bearing potential agree to use double barrier method of contraception
b) Female patients of non-child bearing potential must meet one of the following criteria:
 - Postmenopausal for at least 1 year, or
 - Documented oophorectomy or hysterectomy, or
 - Surgically sterile
5. Willing and able to understand and sign the informed consent.

6.2.2 Exclusion Criteria

Fracture-Specific Exclusion Criteria

1. Index treatment is greater than 28 days post fracture.
2. Open fractures with severe contamination.
3. Extremely comminuted fractures where insufficient holding power of the balloon on the intramedullary canal is probable.
4. Marked bone loss or bone resorption: patients, who due to a prior delayed union or non-union of the bones or other illnesses, may not be able to have their fracture adequately reduced prior to placement of the IlluminOss-device. This could leave bone void spaces that would preclude the device from maintaining alignment of the fractured bone.
5. Previous fracture of affected limb.

General Exclusion Criteria

6. Pregnant or lactating.
7. Active or incompletely treated infections that could involve the site where the device will be implanted.
8. Distant foci of infections that may spread to the implant site.
9. Uncooperative patients or patients who are incapable of following directions (for example as a consequence of a neurological or psychiatric disorder).
10. Concomitant metabolic disorders that may impair bone formation.
11. Osteomalacia.
12. Allergic to implant materials or dental glue.
13. Vascular insufficiency, muscular atrophy, or neuro-muscular disease.
14. Polytrauma patients (multiple injuries resulting from a high impact event, eg- a motor vehicle accident).

15. Life expectancy less than one year due to concurrent illness.

6.2.3 Criteria and procedures for subject withdrawal or continuation

6.2.3.1 Conditions for Discontinuation

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

6.2.3.2 Data Collection and Follow-up for Discontinued Patients

If a patient 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 at the end of the study. If termination was the result of an AE or death, the appropriate AE forms and/or notifications will ensue. In as much as possible, every attempt will be made to conduct an exit/final visit prior to termination from the study. If possible, permission for contact to assess long-term outcomes should be obtained.

6.2.3.3 Patients Lost to Follow-up

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

6.2.4 Enrollment

A subject is considered enrolled in the clinical investigation after they have provided informed consent and once the sheath has crossed the fracture site. Subjects who fail one or more of the eligibility criteria are considered screening failures and are exited from the study.

6.2.5 Duration of the Study

The enrollment period is expected to take approximately 10 months. Subjects are being followed for one year after treatment. The total duration of the clinical investigation is thus expected to take approximately two years, including the enrollment period.

6.2.6 Number of Subjects

An estimated 45 subjects will 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.

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 post-marketing study was not statistically determined. The Sponsor decided that 30 subjects need to be enrolled and followed through 12 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. Due to potential enrollment failures and loss-to-follow-up, it was decided that 45 patients will be sufficient to ensure that at least 30 subjects are followed through 12 months.

7.3 Analysis Population

The Intent-to-Treat (ITT) analysis population is defined as all patients 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, osteoporosis history, smoking history, hand dominance, and fracture characteristics.

7.5 Analysis of Primary Endpoint

The proportion of patients who are confirmed to have achieved normal healing (at least 2 of 4 cortices or at least 2 of 4 views demonstrating bridging on standard radiographs) by the Day 180 Visit will be presented, along with the corresponding 95% binomial confidence intervals. If the proportion of patients with normal fracture healing at the Day 180 Visit is at least 90% then the primary endpoint will be met.

7.6 Analysis of Secondary Endpoints

7.6.1 Fracture Healing

The proportion of patients who are confirmed to have achieved complete healing by the Day 180 Visit, the proportion of patients who are confirmed to have achieved normal healing by the Day 360 Visit, and the proportion of patients who are confirmed to have achieved complete healing by the Day 360 Visit will be presented along with the corresponding 95% binomial confidence intervals.

7.6.2 Procedure- and Device-related Complication Rate

The proportion of patients who experience a procedure- or device-related complication by the Day 180 Visit will be presented along with the corresponding 95% binomial confidence intervals.

7.6.3 Duration of Index Procedure and Length of Hospital Stay

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

7.6.4 No Pain at Palpation

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

7.6.5 Return to Pre-Fracture Mobility

The number and percentage of patients who return to pre-fracture mobility will be presented at each follow-up visit.

7.6.6 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.

7.6.7 DASH Score

Summary statistics of the DASH scores will be presented at baseline and each follow-up visit for those patients on whom questionnaires were completed. Additionally, change from baseline will be presented at each follow-up visit.

7.6.8 Constant Shoulder Score

The number and percentage of patients in each Constant Shoulder Score category (Poor, Fair, Good, and Excellent) will be displayed for those patients on whom the score is available. A shift table will be used to summarize changes from baseline to all follow-up intervals.

7.6.9 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 patients for each level of these ordinal variables will be displayed.

7.6.10 Disability Status

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

7.6.11 Return to Work

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

7.6.12 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 180 and Day 360. 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 in section 7.5 and 7.6 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 patients who used supportive orthopedic devices post-surgery and who used prescription and over-the-counter analgesic medication will be presented.

7.8 Endpoint/ Interim Analysis

There will be an endpoint/interim analysis conducted for this study when the last patient completes his/her Day 180 visit and the data for all patients through the Day 180 Visit are locked. The interim analysis will include the analyses of the primary endpoint, all secondary endpoints, and all health economic data using data collected by the Day 180 Visit. As the analyses are descriptive, no adjustments to the confidence intervals are deemed necessary as a result of the interim analysis for this single arm study.

7.9 Schedule of Activities and Patient Evaluations

An overview of the study-specific procedures per visit is presented in Appendix 2. Study subjects will have a maximum of eight visits to the hospital/clinic during the study.

All testing should be conducted at the investigational site. Follow-up testing may be performed at another site only if it is not possible for the patient to return to the investigational site. In such cases, the principal investigator may arrange for the study-required testing to be completed by the patient's local physician. However, it remains the responsibility of the study principal investigator to ensure collection of appropriate information. Copies of source documents from the local physician must be obtained and kept in the patient's study file.

7.10 Visit 1: Screening and Baseline

7.10.1 Screening

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

All potential patients will be screened for eligibility and 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 excluding the patient if the patient does not satisfy the initial eligibility criteria. The log will also be used to document enrollment failures. This includes patients who sign the ICF and subsequently meet an exclusion criterion (e.g., placement of device is not successful).

7.10.2 Baseline

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

A clinical assessment will be performed as follows:

- Inclusion and exclusion criteria review;
- Medical history, including smoking history, osteoporosis history, work status, and whether the subject has any disabilities, with a focus on the fracture event;
- Physical exam, with focus on target limb, including neurovascular

- exam, including OA grading of fracture and Gustillo grading of soft tissue;
- Urine pregnancy test (if applicable);
 - Concomitant medications, including pain medication history of use;
 - Disability of the Arm, Shoulder and Hand (DASH) score (optional);
 - Constant shoulder score (optional);
 - Patient-completed pain VAS; and
 - Radiographs of target fracture.

Note: Standard institutional measures for protection against radiation should be adhered to when obtaining radiographs.

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.

7.11 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 patient ineligible for study participation, the patient should not be treated with the IlluminOss device. The patient should receive the standard of care as determined by the surgeon.

The IFU outlines the full procedure along with the device preparation guidance.

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 Photodynamic Bone Stabilization System.

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 bone pin used);
- AE assessment;
- Use of pain medications;
- Return to pre-fracture mobility;
- Date of discharge.

Note: If placement of the IlluminOss Photodynamic Bone Stabilization System is attempted but not successful, the patient should receive the standard of care as determined by the surgeon. This patient is considered an enrollment 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

The investigator shall determine the post-operative management of the fracture.

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

A removable, external splint may be used as clinically indicated, per standard hospital protocol. The use of external casting or other stabilizing technologies is discouraged, unless the investigator believes it is clinically warranted.

Visits 1 and 2 may occur during the same day if acute stabilization of the fracture is required. This is at the discretion of the principal investigator. It should be noted that taking informed consent should always be done prior to screening and surgery.

7.12 Follow-up Visits and Evaluations

Follow-up evaluations will be scheduled for 7-14, 30, 60, 90, 180, and 360 days post-index procedure.

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

The following will be performed:

- AE assessment;
- Concomitant medications;
- Total active (TAM) and passive (TPM) range of motion, performed as tolerated (if target arm is not externally casted/splinted, etc.);
- Clinical assessments that include, but are not limited to, assessments for pain, return to pre-fracture mobility, return to work, disability status, use of pain medication and physical therapy prescription status;
- Disability of the Arm, Shoulder and Hand (DASH) score (optional);
- Constant shoulder score (optional);
- Patient-completed pain VAS; and
- Radiographs of target fracture.

Note: standard institutional measures for protection against radiation should be adhered to when obtaining radiographs.

If available, additional health economic data may be obtained.

7.12.2 Visit 4 and 5: 30-day Follow-up (± 14 days) and 60-day Follow-up (± 14 days)

The following will be performed:

- AE assessment;
- Concomitant medications;
- TAM and TPM (as tolerated, and if target arm is not externally casted/splinted, etc.);
- Clinical assessments that include, but are not limited to, assessments for pain, return to pre-fracture mobility, return to work, disability status, use of pain medication and physical therapy prescription status;
- Disability of the Arm, Shoulder and Hand (DASH) score (optional);
- Constant shoulder score (optional); and
- Patient-completed pain VAS.

If available, health economic data may be obtained.

7.12.3 Visits 6, 7, and 8: 90-day Follow-up (± 14 days), 180-day Follow-up (± 30 days), and 360-day Follow-up (± 60 days)

The following will be performed:

- AE assessment;
- Concomitant medications;
- TAM and TPM (as tolerated, and if target arm is not externally casted/splinted, etc.);
- Clinical assessments that include, but are not limited to, assessments for pain, return to pre-fracture mobility, return to work, disability status, use of pain medication and physical therapy prescription status;
- Disability of the Arm, Shoulder and Hand (DASH) score (optional);
- Constant shoulder score (optional);
- Patient-completed pain VAS; and
- Radiographs of target fracture.

Note: standard institutional measures for protection against radiation should be adhered to when obtaining radiographs.

7.13 Activities Performed by Sponsor Representatives

One or more technical representatives of the sponsor may be present during implantation of the device at the request of and under supervision of the principal investigator.

8 Adverse Events, Adverse Device Effects and Device Deficiencies

8.1 Definitions

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether it is considered investigation medical device related or not.

NOTE 1: This includes events related to the investigational device or the comparator.

NOTE 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).

NOTE 3: 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 subject and may require additional therapy;
- Moderate: an AE that interferes with the subject's activities and requires intervention or additional therapies;
- Severe: an AE that is intolerable, or necessitates additional therapy, or places the subject at immediate risk of harm.

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

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

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the

Clinical Investigational Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Device Deficiency: A device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

Adverse Device Effect (ADE): Adverse event 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): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE): an AE is considered to be an unanticipated adverse device effect if there is an occurrence of a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Device Related Adverse Event: an AE is considered to be device related when, in the judgment of the Principal Investigator, 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 Adverse Event: an AE is considered to be procedure related when, in the judgment of the principal investigator, it is reasonable to believe that the event is associated with the IlluminOss 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 Adverse Event: an AE is considered to be concomitant medication related when, in the judgment of the principal investigator, 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 Adverse Event: an AE is considered to be related to a pre-existing condition when, in the judgment of the principal investigator, 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 required to be documented as AEs because they are normally expected to occur in conjunction with the device-implant and/or removal procedures, or are associated with customary, standard care of patients undergoing surgical procedures for treatment of arm fractures:

- Early post-operative pain (within 72 hours post-index procedure) at the access site and/or related to position on procedure table;
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 hours post-index procedure);
- Electrolyte imbalance without clinical sequelae following index procedure, even if requiring correction;
- Systolic or diastolic blood pressure changes that do not meet the definition of hypotension or hypertension;
- Low grade temperature increase ($\leq 38.3^{\circ}\text{C}$ / $\leq 101^{\circ}\text{F}$) 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, in duration, 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 principal investigator at the investigational site should utilize his/her own clinical judgment in evaluating patient AEs, and may determine that the above events should be reported as AEs.

The principal investigator should follow all unresolved SAEs until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, or the AE is otherwise explained.

8.2 Relation to the Device and Procedure

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

Not related

An adverse event for which sufficient information exists to indicate that there is no causal connection between the event and the device or procedure. The adverse event 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 adverse event may not follow a reasonable temporal sequence following the treatment procedure.

Possibly related

There is a reasonable possibility that the adverse event may have been primarily caused by the device or procedure. The adverse event 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 device or the procedure.

Probably related

There is a reasonable probability that the adverse event may have been primarily caused by the device or procedure. The adverse event 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 adverse event has a strong causal relationship to the device or procedure. The adverse event 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.

8.3 Reporting to Sponsor

All adverse events classified as serious adverse events and/or unanticipated adverse device effects shall be reported by the principal investigator (or designee) to the study Sponsor or Medpace via telephone (+31 43 3063320), email (safety.mmd@medpace.com) or facsimile (+31 43 3063338) within 24 hours of learning of the SAE/UADE.

The principal investigator (or designee) shall send a written report, including a narrative description of the serious and/or unanticipated adverse device event, to the Sponsor or Medpace, within three (3) working days of the initial report.

Patient death during the study must be reported by the principal investigator (or designee) with written documentation by facsimile to Medpace within 24 hours of the principal investigator'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's authorized representative, Medpace, within ten (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 principal investigator will be required regarding the reasons why.

8.4 Reporting to Ethics Committee and Competent Authority

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 the Netherlands, the sponsor (or its representative Medpace) will report the SAEs through the web portal ToetsingOnline to the accredited EC that approved the protocol:

- Immediate (within 2 calendar days of first knowledge) for SAEs where there's an imminent risk of death, a serious injury or illness which also requires adequate action for other patients or subjects
- Within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events
- Quarterly via MEDDEV table

8.5 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 principal investigator (or designee). The report should include: severity, duration, treatment used, treatment outcome and the principal investigator'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 lab studies) must be sent to the Sponsor or designee to describe the treatment, duration, resolution or outcome of the AE.

The following criteria must also be adhered to by the principal investigator:

- Use separate AE form(s) to document each series of events;
- The AE form(s) must be signed by the principal investigator or sub-

investigator;

- It is the responsibility of the principal investigator to inform the EC of SAEs as required by the EC procedures.

8.6 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.

8.7 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

9 Administrative Issues

9.1 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, requirements of the approving EC, ISO14155 and other applicable regulatory requirements. Any additional requirements imposed by an Ethics Committee or regulatory authority will be followed, as appropriate.

9.2 Insurance

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

9.3 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 patient 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 patient, or which may adversely affect the scientific validity of the study.

Prior to first patient enrollment, a signed copy of the EC's favorable opinion letter identifying the clinical study and investigational site is required to be submitted to Medpace, 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 Medpace.

9.4 Informed Consent

If the patient meets all clinical eligibility criteria, the patient 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 patients 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 patient's medical records and study files. A copy of the informed consent form must be given to each patient 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.

9.5 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 patient.

9.6 Device Removal

In the event the principal investigator deems it necessary to remove the implanted IlluminOss device, the patient will undergo the standard x-rays required in the protocol both prior to and following device removal.

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

9.7 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 principal investigator.

9.8 Data Monitoring and Quality Control

Medpace is the clinical research organization (CRO) assigned to manage the data for the investigational study on behalf of the Sponsor, IlluminOss Medical.

9.8.1 Training

The training of the PI will be the responsibility of the Sponsor, IlluminOss Medical, with the assistance of Medpace. 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 Segment: The didactic session will be comprised of a presentation reviewing the concepts of the protocol and a review of any clinical information using the PBSS device. In addition, the team will be shown a presentation on the surgical technique as well as the removal technique in the event the product needs 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 in-vitro modeling will be used for the clinician to gain a better understanding of the system operation as needed.

9.8.2 Case Report Forms

Paper Case Report Forms (CRFs) will be used to collect all patient data during the course of the study, and should be signed by the Principal Investigator when complete.

Good Clinical Practice Guidelines require that principal investigators maintain information in the study patient'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 study 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 principal investigator, study name, patient number assigned and a statement that consent was obtained;
- Dated and signed notes from each study patient visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams);
- Information related to AEs;
- Study patient's condition upon completion of or withdrawal from the study;

- Discharge summaries/procedure reports.

9.8.3 Data Reporting

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

The principal investigator is required to sign the CRF on the appropriate page(s) to verify that he/she has reviewed the recorded data. 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 an IlluminOss Medical appointed independent monitor from Medpace and at the investigational site at regular intervals throughout the study. The investigator will allow the monitor and/or representative of the Sponsor, and the FDA or other regulatory authorities to review and inspect the study files, patient CRFs, patient medical records and other related study documents, as required.

9.8.4 Data Review

All CRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the monitor and will be retrieved, clarified and entered by study personnel as necessary throughout the study. IlluminOss Medical or Medpace may request additional documentation from the principal investigator, 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 Medpace. Medpace will also be responsible for the quality control of the database and confirming the overall integrity of the data.

9.9 Record Maintenance

Principal Investigator files containing all records and reports of the investigation should be retained for a minimum of two (2) years or longer (depending upon national requirements) after the completion/ termination of the investigational study. They may 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.

9.10 Investigational Site Monitoring

Medpace is the Contract Research Organization responsible for the monitoring of the study. The study will be monitored according to applicable provisions of Medpace's clinical monitoring procedures and in compliance with European health authority regulations.

9.11 CIP Amendments

Amendments to this protocol will be submitted to the ethics committees and competent authorities for review. The intended changes may only be implemented after approval of such an authority.

9.12 Deviations from Clinical Protocol and Medical Emergencies

The principal investigator 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 patient's risk or affect the validity of the study. In medical emergencies, prior written approval for protocol deviations will not be required, but Medpace, 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 EC in accordance with their specific EC reporting policies and procedures.

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

9.13 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, EC, 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 patients.

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 Ethics Committees and if necessary the regulatory authority(ies), 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 patients will continue to be followed for the duration of the study.

10 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 investigation subject only to compliance with regulatory requirements pertaining to subject protected health information.

The Sponsor, IlluminOss Medical or their authorized agent, Medpace, will be responsible for notifying the health authority within 30 working days of the completion/termination of the investigation and shall submit a final report to the health authority and all reviewing ECs and participating principal investigators within 6 months after study completion/termination.

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12 Appendices

Appendix 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/ DIC (disseminated intravascular coagulation), 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.

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 emboli and thromboemboli): The blockage of a blood vessel by an embolus, which can include a thrombus or an air bubble.

Hematoma: Collection of blood (or serous fluid) at the operative site which 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) which 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, 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 causing 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 or splitting of the layers of the surgical wound, not associated with infection.

Appendix 2: Schedule of Activities

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Screening and Baseline	Surgery and Discharge	7-14 Day F/U (+ 3 days)	30 Day F/U (± 14 days)	60 Day F/U (± 14 days)	90 Day F/U (± 14 days)	180 Day F/U (± 30 days)	360 Day F/U (± 60 days)
Inclusion/Exclusion Review	X							
Informed Consent	X							
Patient Medical History	X							
Physical Exam	X							
Clinical Assessments ¹			X	X	X	X	X	X
Disability of the Arm, Shoulder and Hand (DASH) Score ³	X		X	X	X	X	X	X
Pain Visual Analog Scale (VAS)	X		X	X	X	X	X	X
Constant Shoulder Score ³	X		X	X	X	X	X	X
Total Active & Passive Range of Motion			X ²	X ²	X ²	X ²	X ²	X ²
Radiographs of Fracture	X		X			X	X	X
Adverse Events		X	X	X	X	X	X	X
Health Economic Assessment	X	X	X	X	X	X	X	X

¹ Clinical assessments include, but are not limited to, assessments for pain, return to pre-fracture mobility, return to work, disability status, use of pain medication and physical therapy prescription status.

² Assessment performed as tolerated.

³ The Disability of the Arm, Shoulder and Hand (DASH) Score and the Constant Shoulder Score are optional assessments at each follow-up visit. If the scores are taken at baseline, every effort should be made to take scores at the subsequent visits.