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CLINICAL INVESTIGATION PLAN
CIP ID: CSE2014-08T

Zimmer® MotionLoc® in Distal Tibia Fractures: An Observational Study

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FINAL

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This protocol contains CONFIDENTIAL information and should be restricted in its distribution

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I. Protocol Synopsis

Title:	Zimmer MotionLoc in Distal Tibia Fractures: An Observational Study
Sponsor:	Zimmer Biomet, Warsaw, Indiana
Protocol Number:	CSE2014-08T
Objectives:	The objective of this observational prospective study is to systematically document the clinical outcomes of Zimmer MotionLoc Screws for Periarticular Locking Plate System applied to distal tibia fracture treatment and confirm safety and performance of the screws.
Endpoints:	**Primary endpoint:** Radiologic & clinical fracture healing at three months post-surgery. **Secondary endpoints:** • Complications • Radiologic & clinical fracture healing at 6 weeks, 3, 6, and 12 months post-surgery. • Callus size & distribution at 6 weeks, 3, 6, and 12 months post-surgery.
Target Population:	Patients with distal tibia fractures (AO 43-A and C) requiring surgical intervention eligible for locked plating.
Study Design:	Prospective, global, multi-center, non-randomized, non-controlled
Number of Cases:	Patient enrollment is limited to one year or 40 subjects whichever is reached first. Per site enrollment will be limited to 15 subjects.
Length of Study:	2 years (1 year enrollment plus 1 year follow-up): Required follow-up visits at 6 weeks, 3, 6, and 12 months post-surgery.
Study Device:	*Zimmer*® Periarticular Distal Tibial Locking Plates (medial and/or lateral) in conjunction with *Zimmer*® *MotionLoc*® Screw for the Periarticular Locking Plate System.
Scores:	FIX-IT
Documentation:	Electronic Case Report Forms
Statistical Reporting:	Data collected will be summarized and reported to each participating investigator. Statistical analysis will be conducted by Zimmer Biomet or its designee.

II. Introduction

The optimal treatment for distal tibia fractures remains controversial. A recent systematic literature review found a reduced risk for malalignment for plate fixation compared to intramedullary nailing [2]. However, for bone union, wound complications and superficial infection or deep infection no statistically significant differences were identified.

In the last decade locking plates gained popularity not only for distal tibia fractures but fracture treatment in general. Recent studies raised concerns because of the inherent stiffness of these locking devices and found they might suppress fracture healing [3][4][5]. To address this issue the concept of Far Cortical Locking (FCL) was developed [6][7] and has been commercially available since 2010 in the *Zimmer MotionLoc* Screw for NCB® Polyaxial Locking Plate System and since 2014 in the *Zimmer MotionLoc* Screw for *Zimmer* Periarticular Locking Plate System (Zimmer Inc.).

FCL screws lock rigidly into the plate and into the far cortex, but retain a controlled motion envelope in the near cortex. The screws have an elastic shaft portion that can deflect within this motion envelope. This flexion of FCL screw shafts induces symmetric axial motion at the fracture site in response to load bearing. FCL screws are optimized to reduce the initial stiffness of a locked plating construct while retaining its construct and fixation strength. *MotionLoc* Screws for *Zimmer* Periarticular Locking Plate System reduce the locked plating construct stiffness by more than 58% while retaining construct strength [8].

Recently, a prospective observational clinical study in 31 distal femur fractures treated with *Zimmer MotionLoc* Screws for *NCB* Polyaxial Locking Plate System has shown a fracture healing rate of 97% (30 out of 31) after a 6 month follow up period with no implant and fixation failure.

The purpose of this observational prospective study is to systematically document the clinical outcomes of *Zimmer MotionLoc* Screws for Periarticular Locking Plate System applied in distal tibia fracture treatment and confirm safety and performance of the screws.

III. Study Objectives

The objective of this observational prospective study is to systematically document the clinical outcome of *Zimmer MotionLoc* Screws for Periarticular Locking Plate System applied in distal tibia fracture treatment and confirm safety and performance.

Primary Endpoint:

- Radiographic & clinical fracture healing at 3 months post-surgery.

Secondary Endpoints:

- Complications
- Radiologic & clinical fracture healing at 6 weeks, 3, 6, and 12 months post-surgery.
- Callus size & distribution at 6 weeks, 3, 6, and 12 months post-surgery.

Radiologic fracture healing is defined as bridging of three of the four cortices as seen on x-ray/CT [10][11]. Clinical healing will be assessed using the Function Index for Trauma (FIX-IT) [12]. The

FIX-IT instrument quantifies clinical healing by assessing weight-bearing and fracture site pain on an ordinal scale. It has been initially validated in patients with tibia and femur fractures [12].

Callus size of the anterior, posterior, and medial aspect will be assessed for each time point using a validated and published computational method [13].

IV. Study Device

Description of the Device

Zimmer MotionLoc is a screw technology developed to reduce construct stiffness of locking plates while retaining construct strength. Further, it creates constructs that allow nearly parallel interfragmentary motion compared to standard locking screws constructs which allow motion under load at the far cortex while motion at the near cortex remains negligible. The parallel interfragmentary motion creates an environment that is thought to promote a symmetric callus [9].
The *Zimmer MotionLoc* screw is designed for use with *Zimmer*'s Periarticular Locking Plate System. In this trial the 3.5mm diameter stainless steel version will be used. The screw is available from 22 to 44mm and 22 to 60mm length in two millimeter increments, non-sterile and sterile, respectively. The *Zimmer MotionLoc* Screw for the Periarticular Locking Plate System (Figure 1) has a standard cortical thread section (self-tapping, single helix); an expansion section, intended to create the gap for motion in the near cortex; a mid-section thread with a reduced core-diameter and reverse cutting flutes to aid in screw removal; a non-threaded collar section; and a double lead threaded head for engagement in the plate.

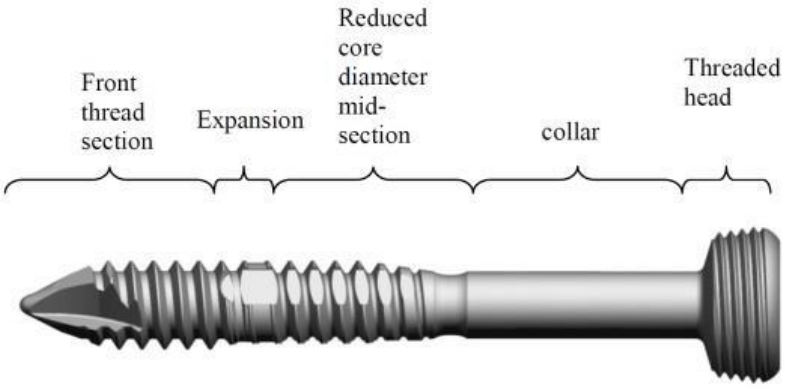

Figure 1: *Zimmer MotionLoc* Screw for the *Zimmer* Periarticular Locking Plate System

Further product information is available in the surgical technique or instruction for use (see investigator binder).

V. Study Design

General Study Design

This study is designed to be prospective. It is a multi-center, global, non-randomized, and non-controlled study. Institutional Review Board/Ethics Committee (IRB/EC) approval for each clinical site must be obtained prior to conducting this research. The primary outcome will be clinical & radiological fracture healing at three months post-surgery.

Study Duration

After the initial visit followed by surgery, the patient is expected to participate in the study for a time period of one year. With estimated enrollment duration of one year the estimated overall study duration will be two years.

Study Population

The study population consists of maximally 40 subjects with distal tibia fractures. Subject enrollment is limited to one year or 40 subjects, whichever is reached first. If after one year less than 30 subjects are enrolled, enrollment will be continued until 30 subjects are enrolled.

Number of Subjects, Number of Sites

A maximum of 40 subjects will be enrolled at about 8 study sites. Per site enrollment will be limited to 15 subjects.

Data Collection Overview

	FORM / TIMEPOINT					
	Baseline (pre-operative and surgery data)	**Post-operative until Discharge**	**6 weeks ± 14 days**	**3 months ± 14 days**	**6 months ± 30 days**	**12 months ± 30 days**
ASSESSMENT						
Patient Demographics/ Details	✓					
Surgery Details	✓					
Clinical	✓	✓	✓	✓	✓	✓
X-ray operated side AP and lateral view	✓	✓	✓	✓	✓	✓
CT operated side				✓		
FIX-IT (surgeon)			✓	✓	✓	✓
Patient Withdrawal/ Lost to Follow-up/ Study Completion		✓ if applicable	✓ if applicable	✓ if applicable	✓ if applicable	✓
Protocol Deviations	✓ if applicable	✓ if applicable	✓ if applicable	✓ if applicable	✓ if applicable	✓ if applicable
Complications	✓ if applicable	✓ if applicable	✓ if applicable	✓ if applicable	✓ if applicable	✓ if applicable

VI. Study Procedures

Patient Inclusion / Exclusion Criteria

Inclusion Criteria

- Male and female
- Age: 18 years or older
- Primary distal tibia fractures (AO 43-A and C) requiring surgical intervention eligible for locked plating
- With or without fibula fracture involvement (treated or not treated by osteosynthesis)
- Close or open fractures Gustilo type I
- Unilateral or bilateral fractures
- Patients who are capable of understanding the doctor's explanations, following his instructions and are able to participate in the follow-up program.
- Patients who give written consent to take part in the study by signing the "Patient Consent Form".

Exclusion Criteria

- Delay of surgery for more than two weeks.
- Open fractures Gustilo type II & III
- History of infection of the affected extremity
- Non-ambulatory patients
- Planned fixation strategy includes interfragmentary lag screw fixation of non-articular fractures.
- Addition of bone graft, bone graft substitute or BMP.
- Immobilization with plaster.
- Likely problems with maintaining follow-up program (e.g. patients with no fixed address, plans to move during course of study)
- Not expected to survive the duration of follow-up program.
- Patients known to be pregnant or breastfeeding.
- Patients who are unwilling or unable to give consent.

Product contraindications:

- All concomitant diseases that may impair the fixation of the implant and/or the success of the intervention.
- Acute or chronic, local or systemic infections.
- Severe muscular, neural, or vascular diseases that endanger the extremities involved.
- Lack of bone substance or bone quality, which makes stable seating of the screws impossible or results in an unstable screw/plate construct.
- Allergy to the implanted material.

Patient Screening

All consecutive patients with distal tibia fractures presenting to the participating study centers will be identified, screened for eligibility and documented on the Screening Log included in the Regulatory Binder.

Informed Consent

All patients must sign the most recent Informed Consent Form prior to formal screening and study participation. All patients who are invited and agreed to participate in the clinical study must sign a written Informed Consent approved by the EC/ IRB. Prior to performing any study related treatment, the Investigator will discuss details of the study with the patient and hand out the Patient Informed Consent Form. During the Informed Consent process, the Investigator must introduce the patient to the clinical study by providing and explaining the Patient Information Form, and describing the study procedures, alternative treatments, risks and benefits of the participation as well as how the data will be handled and protected. If the patient decides, after the Investigator's explanations and after receiving adequate time to read the Patient Information Form, to participate in the clinical study, she/he must fill in and sign the Patient Consent Form. No patient will be enrolled without signing the Informed Consent. Any new significant information on the study device or the study which may be relevant to the patient's willingness to participate or to continue participation in the study will be provided to new and existing patients throughout the clinical study.

Informed Consent Log

An Informed Consent Log must be maintained throughout the study. All patients who are consented for the study must be entered in the log regardless of eligibility. In the event subjects must sign additional study-required consent forms after enrollment, per IRB/EC or other requirements, subsequent consents must be entered in the Informed Consent Log as well.

Determination of Eligibility

Patient eligibility for enrollment will be determined for consenting candidates based on the inclusion/exclusion criteria. Patients must meet all of the inclusion criteria and none of the exclusion criteria in order to be offered enrollment into the study. Determination of eligibility may include an interview to assess significant patient surgical/medical history, history of present illness/injury, evaluation of present pain and functional capacity, and a radiographic assessment. All eligible patients will be offered enrollment into the study. For the purposes of this clinical study, patients will be considered subjects after enrollment has been completed.

Subject Enrollment Log

A Subject Enrollment Log must be maintained throughout the study and is included in the Investigator Binder. All patients enrolled in the study must be entered into the Enrollment Log and the "Inclusion/Exclusion" form must be completed. Patients must be entered into the Enrollment Log sequentially.

Baseline/Preoperative Assessment

Following enrollment, demographic and injury classification data will be entered into the "Demographic Information & Injury Classification" set of forms.

Surgical Technique

Implantation will be performed in accordance to the manufacturer's surgical technique. The distal articular segment will be fixed to the plate(s) (medial and/or lateral *Zimmer* Periarticular Distal Tibial Locking Plate) with the appropriate number of standard locking screws. All fractures will be treated with a "bridge plating" strategy - working length (empty screw holes between the distal and proximal segment, see Figure) is up to investigator/surgeon discretion. A minimum of three MotionLoc screws will be applied into the proximal shaft segment. No inter-fragmentary lag screws are permitted across non-articular fractures.

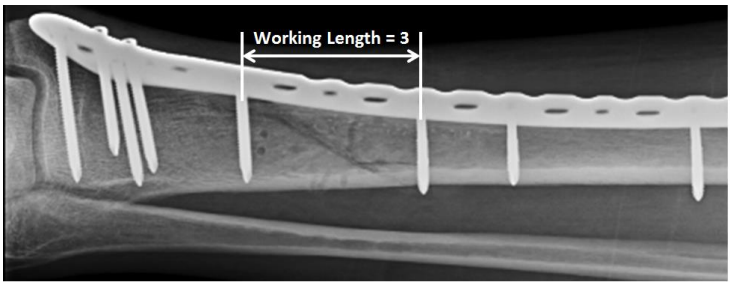

Figure 2: Working length

After surgery, intraoperative data will be entered into the "Operative Information" set of forms.

Postoperative Care

Weight bearing will be at the surgeon's discretion based on the degree of fracture healing.

Surgery until Discharge

After surgery, but before the subject leaves the hospital, standard anterioposterior and lateral x-rays of the operated side must be obtained and the "Discharge" set of forms must be completed.

Follow-up Procedures (Data Collection)

Follow-up evaluations will be performed at 6 weeks (± 14 days), 3 months (± 14 days), 6 months (± 30 days) and 12 months (± 30 days) post-surgery. Standard anterioposterior and lateral x-rays of the operated side must be obtained at each follow-up. If the treating surgeon is unable to adequately assess cortical healing due to radiographic obstruction of the implant(s), additional x-ray(s) should be performed. At 3 months a CT scan of the fracture site must be performed in addition. The "Follow-up" set of forms must be completed at each follow-up time point. This includes the assessment of radiologic fracture healing. At 6 weeks, 3, 6 and 12 months, the surgeon must assess the FIX-IT Score and document on the corresponding set of forms. At the 12

month follow-up the "Study Completion" form must be completed additionally. Copies of the original x-ray films and CT scans must be sent to the Sponsor.

Patient Withdrawal

Patient withdrawal has to be documented on the "Study Completion" form. In particular the reason for withdrawal must be documented. The occurrence of any of the following situations gives reason to withdraw a patient from the study:

- Voluntary patient withdrawal. Patients are at liberty to withdraw from the study at any time and for any reason without affecting future treatment.
- Development of a concurrent condition which would interfere with the patient's continued participation.
- Reoperation including complete removal of study device(s).
- Patient is non-compliant.

Lost to Follow-up

Patients will be considered lost to follow-up after they have missed a visit and a reasonable number of attempts to locate and evaluate them have failed. This has to be documented on the "Study Completion" form and in particular the reason should be documented. Patients lost to follow-up will not be replaced within the study.

Minimization of Subjects Lost to Follow-Up

Subject follow-up is extremely important for the conduct of a clinical study. The expectation is to maintain the highest rate of follow-up compliance possible throughout this study. No replacement is foreseen for any patient lost to follow-up. In an effort to minimize lost-to-follow-up subjects, the following recommendations and/or study requirements are essential to ensure proper patient selection and compliance:

1. Patient Eligibility: Subjects will be selected according to the inclusion/exclusion criteria detailed in Section 8 and are expected to return for all follow-up visits.
2. Patients Counseled: Patients will be counseled during the Informed Consent process on the importance of returning for follow-up visits.
3. Patient Exclusion: Patients who are not willing to return for study required follow-up visits and/or are not willing to comply with the follow-up schedule will not be considered for enrollment into the study.
4. Subject Due Listings: In addition to proper patient selection, Zimmer Biomet will provide subject due notices to the sites on a regular basis in order to track each study participant and monitor adherence to the required follow-up visit timeframes. The subject due listings will facilitate scheduling the subjects for their return office visits.
5. Contact Tracking: Attempts to contact subjects will be documented in the study subject's medical record. It is recommended that the first three attempts be made by telephone. If

after three calls, contact has not been successful, the below is required prior to terminating the study subject from the study:

Recommended Contact Attempts

If	Then
a response is not received from 3 phone calls	the investigator should send a letter to the subject explaining the follow-up agreement per informed consent.
a response is not received from the investigator's first letter	the investigator should send a certified letter to the subject.
a response is not received from the investigator's certified letter	the investigator should use any additional contacts provided by the subject to contact the subject.
all attempts to contact the subject are unsuccessful or the subject is contacted and chooses to withdraw from the study	the "Study Completion" form will be completed and will specify the reason the subject is no longer participating in this study.

Radiographic Management

All radiographic imaging performed according to the protocol will be reviewed and evaluated by the investigator or qualified designee at the time of the post-operative assessment for standard patient management purposes. If a radiographic adverse event is identified by the Investigator during the course of the investigation, the Investigator must document the event and report the radiographic findings on a Complication Case Report Form for Sponsor review. It is possible that radiographs taken within this study could be used for future regulatory submissions and/or product evaluations, and may therefore require radiographic review by an unbiased independent review.

Recommended Revision Procedure

If a device has to be removed[1], the investigator will choose the best revision treatment method for the subject. Before revision surgery, the Investigator must document any significant radiographic findings related to the need for revision. Additionally, once the revision surgery has been completed, the Investigator must complete an Adverse Event CRF, as well as a Study Completion CRF, terminating the subject from the study.

[1]Device removal after fracture healing, upon patient request or as part of standard treatment, is not considered a "Recommended Revision Procedure".

Explanted Device Return

All components removed, except the devices removed after fracture healing upon patient request or as part of standard treatment, should be returned to Zimmer Biomet for analysis. The Investigator must notify the Clinical Study Manager prior to the return of any device. Properly prepared specimens are to be sent to:

Zimmer Biomet
Attention: Product Services Department
1777 W. Center St.
Warsaw, IN 46580

VII. Statistical Methods

General Statistical Methods

Considering the inclusion and exclusion criteria, per study site an enrollment of 5 patients in one year can be expected. Within one year of enrollment at 8 study sites this equals to 40 patients in total. For the purpose of this observational study this number of patients is considered to be sufficient to document first clinical outcome and assess safety and performance. Collected data will be presented descriptively. For categorical data, frequency and percentage will be calculated. For continuous data, mean, standard deviation, median, minimum and maximum will be calculated.

Comparative assessment

For comparative assessments of any non-parametric data (e.g. score between different follow-up time points) the Wilcoxon test will be used for paired, and the Mann-Whitney test for unpaired data. A significance level of p=0.05 will be set.

VIII. Risk Analysis

Zimmer MotionLoc Screws for the *Zimmer* Periarticular Locking Plate System have been commercially available since April 2014. The devices involved are used in accordance with the cleared indications. There are no anticipated risks specific to study participation other than the potential loss of confidentiality. There are no experimental procedures in this study and participation is not anticipated to affect the medical treatment of enrolled subjects.

When used in accordance with product labeling, the risks associated with the used device are similar to those of other locking plate systems used for the same clinical indication or purpose. These risks are either general surgical risks or risks associated with the subject procedure/study device. Unanticipated adverse events can also occur.

A list of adverse events (AE) and anticipated adverse device effects (ADE) can be found in the package insert of the system (see section “Adverse Effects”). Investigators should refer to this list.

All subjects enrolled in the study will have a CT scan of the fracture performed 3 months following surgery. CT scans are frequently used to assess healing because they provide cross-sectional imaging along the entire fracture site; this is particularly useful when orthopaedic implants partially obscure the fracture lines on plain x-ray. In the proposed study, the CT scan will be performed to definitively characterize the healing pattern at the fracture site and to quantify the amount of callus (new healing bone) present. As a result, all subjects will be exposed to the radiation associated with the CT scan of the tibia fracture site at 3 months. The effective dose of radiation from a CT scan of the ankle area is 0.16 ± 0.12 mSv. This is equivalent to two chest x-rays and is a fraction of annual background natural radiation exposure (3 mSv) [14].

Management of Incurrent Events

Any adverse events that occur during the clinical study must be reported to Zimmer Biomet, whether they are device-related or not.

Adverse Events

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Notes:

- This definition includes events related to the investigational medical device or the comparator.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Events

A Serious Adverse Event (SAE) is any AE that:

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

Note: Planned hospitalization for pre-existing condition, or a procedure required in the CIP, without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effects

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device.

Notes:

- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effects

A Serious Adverse Device Effect (SADE) is an Adverse Device Effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is 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 serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Device Deficiency

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

Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Intensity of Symptoms

- **Mild:** the subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or has little clinical significance. The event is not expected to have any effect on the subject's overall health or well-being.

- **Moderate:** The subject has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the subject's health or well-being and may require medical intervention and/or close follow-up.

- **Severe:** The complication interferes considerably with the subject's usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life-threatening. Hospitalization and treatment may be required.

Outcome of Events

The outcome of the event is in relation to the Adverse Event itself, not the treatment rendered (if any) for the event.

- **Resolved:** The outcome of the medical event has been resolved and/or no further treatment is required to treat the reported condition or illness.

- **Tolerated:** The outcome of the medical event will most likely never be resolved. The patient "tolerates" the illness or condition as a matter of life.

- **Pending:** This outcome indicates treatment or diagnostic studies were prescribed for the medical event and the outcome of the medical event is not yet known.

- **Study Withdrawal:** Due to the medical/adverse event, the patient was withdrawn from the study.

- **Device Removal/Reoperation:** The outcome indicates the medical event resulted in the removal of the investigational device or required reoperation of the investigational device.

- **Death:** The outcome indicates the patient death is a direct result of the reported medical/adverse event.

IX. Reporting

The use or disclosure of all protected health information will comply with the HIPAA Privacy Act and Safe Harbor Requirements. All information will be treated with strict adherence to professional standards of confidentiality and will be filed by Zimmer Biomet under adequate security and restricted accessibility by clinical personnel. All reports and communications relating to subjects in the study will identify each patient by the patient's initials, year of birth, assigned study identification number and date of surgery only.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of data reported to the Sponsor in accordance with this protocol. The Investigator or designee will provide periodic reports to their IRB/EC as required to maintain IRB/EC approval throughout the study, and will provide any required final reporting to the IRB/EC upon study completion/termination. A copy of all IRB/EC re-approval letters must be submitted to the Sponsor. If the IRB/EC terminates or suspends its approval of the study, the Investigator or designee will suspend study-related activities and will promptly notify the Sponsor. The Investigator should also promptly provide written reports to the Sponsor and the IRB/EC regarding any changes significantly affecting the conduct of the study, and/or increasing risk to the subjects.

Reporting Prior to Study Start-Up

The following must be submitted to Zimmer Biomet prior to beginning the study.

Clinical Trial Agreement
The Clinical Trial Agreement (CTA) must be signed by all parties to become fully executed. At this point, it must be submitted to Zimmer Biomet prior to the investigator participating in the clinical investigation. The CTA includes the Investigator Agreement.

Institutional Review Board/Ethics Committee Protocol Approval
The protocol must be reviewed and approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the participating surgeon. The investigator may not participate in

the study until the IRB/EC has fully approved the study protocol and a copy of the protocol approval has been received by Zimmer Biomet.

Approved Informed Consent Form

The Informed Consent Form must be approved by the governing IRB/EC before it can be used in the study. The Informed Consent provided to Zimmer Biomet must be date stamped by the IRB/EC; if the IRB/EC does not stamp the approved consent, the consent version must be clearly stated in the IRB/EC approval letter, and visible in the Informed Consent. Each patient must be consented using the most recently approved Informed Consent Form. If the IRB/EC requires an Informed Consent form different than the one provided in the investigational plan, a sample copy of the new Informed Consent form must be submitted to Zimmer Biomet for internal review and approval. Written informed consent must be obtained for each subject before they may be enrolled in the study.

Data Management Plan

Case Report Forms

Data from each subject will be collected on specific Case Report Forms (CRFs) provided for this study. Specific data will be collected at the preoperative, surgical, and postoperative visits. The schedule for data collection is in Section V – Study Design.

Instructions for Case Report Form Completion

All study data will be collected electronically. The Investigator will be responsible for the accuracy and completeness of the CRFs. All data must be completed in the pre-defined CRFs. No items should be left blank unless directed.

The investigator must retain the patient data sources in accordance with local law and regulations. The investigator should take measures to prevent accidental or early destruction of the study related materials. The standard procedures for handling and processing records will be followed per ISO 14155:2011 [1]0, Zimmer Biomet's Standard Operating Procedures (SOPs, Zimmer Biomet QM-System, Warsaw) and the *Data Management Plan for this study.*

Submission of CRFS / X-rays / CT Scans

The CRFs will be submitted electronically via a tool provided by Zimmer Biomet. Anonymized copies of the original x-ray films (JPEG or TIF) and CT scan (DICOM3) taken at the site during the indicated evaluations have to be sent to the Sponsor either via e-mail or post mail (CD or DVD) to the Zimmer Biomet Clinical Study Manager for this study. Alternatively anonymized copies of x-ray films and CT scans can also be provided via Zimmer Biomet representatives within the respective countries.

Data Entry

A central database maintained by the Sponsor will be used to collect and manage the clinical data. Data will be entered directly by site personnel into the clinical database. Data discrepancy (incomplete or inconsistent data) will be raised automatically during or shortly after the data entry,

or manually after data review. They can be addressed directly in the same clinical database by study personnel. The use or disclosure of all protected health information will comply with the data protection act. All information will be treated with strict adherence to professional standards of confidentiality. Data analysis will be conducted at the Corporate Office in Warsaw, Indiana, United States. All data will be encrypted and all personnel in the data management team will comply with the data protection act. All electronic systems are validated according to U.S. Code of Federal Regulation 21 CFR Part 11 and Good Clinical Practice standards. Title 21 CFR Part 11 of the Code of Federal Regulations deals with the FDA (U.S. Food and Drug Administration) regulatory guidelines on electronic records and electronic signatures in the United States. Appropriate audit trails exist on both the front and back end of the data management systems. Back-up files are maintained by the Zimmer Biomet IT department in accordance with 21 CFR Part 11. The database will be subjected to quality control checks and the resulting output will be used to generate data queries. Each participating Investigator will receive study reports on their own data and the collated data for the whole study group. Study metrics, e.g. summary tables, graphical output and descriptive statistics will be produced and may be available as hard copy. Strict confidentiality of individual hospital data will be maintained.

Reporting and Documentation of Adverse Events and Adverse Device Effects

Adverse Events and Adverse Device Effects have to be documented on the Complication form for the duration of the investigation. Further, the outcome of such complications has to be documented on the Complication form and any changes in outcome must be updated during the course of the study.

Reporting and Documentation of Serious Adverse Events, Serious Adverse Device Effects, and Device Deficiencies

Serious Adverse Events, Serious Adverse Device Effects, and Device Deficiencies have to be reported to the IRB/Ethics Committee, according to the timeframe required by the governing IRB/EC guidelines and to the Sponsor as soon as possible. Further, any incidents must be documented on the Complication form for the duration of the investigation. The outcomes of such complications must be documented and any changes in outcomes must be updated during the course of the study.

Protocol Deviations

The investigator should not deviate from the study protocol unless it is to reduce the risk of bringing harm to the patient. If a deviation from the protocol does occur, then the deviation must be documented on the Protocol Deviation CRF. This deviation should be reported to Zimmer Biomet within ten (10) working days of the deviation occurring. All Protocol Deviations must be reported to the governing IRB/EC within the timeframe required by the governing IRB/EC guidelines and to the Sponsor as soon as possible after the deviation has been discovered.

Failure to Obtain Informed Consent

Study subjects must sign an ICF prior to their participation in this study. However, if the Investigator implants a device and enrolls the patient into this study without obtaining informed consent, the Investigator shall submit a completed Protocol Deviation CRF indicating the circumstances for the occurrence to Zimmer Biomet and the reviewing IRB/EC (if applicable) within five (5) working days after the occurrence. The Investigator must obtain informed consent from the patient after discovery of the occurrence before the subject may continue in the study. If an Investigator has recurring failure to obtain patient informed consent, Zimmer Biomet may suspend research activities on an individual basis.

Quality Assurance of Data

The study is conducted in accordance with the Declaration of Helsinki [15] and the ISO 14155:2011 [1]. The Investigator will be required to permit representative(s) of the Sponsor's monitoring team to inspect all Case Report Forms and corresponding sections of the study patients office records and/or hospital original medical records. These audits will be done for quality assurance purposes, i.e. verifying adherence to the Clinical Investigation Plan and the completeness and accuracy of the data being entered on the Case Report Forms.

The Clinical Investigation Plan will be provided to all participating study centers. The Investigators will be fully trained in the proper reporting and submission of trial data prior to patient enrollment.
The Clinical Study Manager is responsible for generating data queries for missing or unclear data if needed. It is the responsibility of the Clinical Study Manager to ensure data quality. There are regular meetings between the Investigators and Zimmer Biomet Clinical Affairs staff. Written correspondence to all sites is used to inform the Investigators of routine study details and to update them on study status.

The Investigator should ensure that all data reported to the Sponsor on the CRFs is accurate and complete. Study records must be retained by the Investigator or Designee for a minimum of 2 years from the Investigator's study termination date, or per applicable regulatory and/or IRB or EC requirements (whichever time period is greater).

Zimmer Biomet Study Monitoring
During the investigation, Zimmer Biomet will conduct periodic monitoring visits and maintain contact with investigators and staff to monitor investigational plan compliance and evidence of subject-related adverse events. These visits will take place as necessary to ensure full compliance by the site. The monitor will report any non-compliance observed at the site to Zimmer Biomet. The monitor will also review the submitted CRFs for completeness, accuracy, and to ensure no increased subject risk has occurred. When any discrepancies are identified, they will be addressed with the investigator or coordinator.

Premature Termination or Suspension of the Study

Zimmer Biomet may decide to suspend or prematurely terminate the clinical study in one or more investigational sites if information that the risk to the study subjects is higher than initially indicated becomes available and/or interim analysis indicates that the results significantly differ from the expected outcomes or statistical endpoints. In the case of an early termination of the study the regulatory authority(ies) and EC(s)/ IRB(s) should be informed according to local and national regulations. The reasons for termination should be provided and documented. Further follow-up of the patients shall proceed according to the hospital standard procedures.

Indemnity
Sponsor shall indemnify participating patients for any damage which may result from the Sponsor's breach of any applicable data protection laws with respect to this Study.

Amendments to the Clinical Investigation Plan

All amendments shall be agreed with the Sponsor and the Investigator(s) and be recorded with a justification for the amendment. Approval of the EC/ IRB that reviewed the original Clinical Investigation Plan must be obtained if required according to the corresponding regulations.

Publication Policy

Both the Clinical Investigator and the Sponsor have the right to publish or allow the results of the clinical trial to be published. The Clinical Investigator recognizes that the Sponsor has a special interest in the results of the clinical study and will, in accordance to the clinical trial agreement, submit manuscripts to the Sponsor prior to submission. If the Sponsor desires changes to be made, these are communicated to the Clinical Investigator for consideration.

Pooled data may be used for training and meetings.

X. References

[1] Clinical Investigation of medical devices for human subjects – Good Clinical practice. ISO 14155:2011

[2] Kwok CS, Crossman PT, Loizou CL. Plate versus nail for distal tibial fractures: a systematic review and meta-analysis. J Orthop Trauma. 2014 Jan 23

[3] Boulton C, Chacko A, Appleton P, Rodriguez E: Factors for Increased failure rate of locked plating in the treatment of distal femoral fractures. Poster presented at the 78th Annual Meeting of the American Academy of Orthopaedic Surgeons, February 15-19, 2011, San Diego, CA.

[4] Gross J, Serna F, Lybrand K, Qui X, Humphrey C, Gorczyca J: Surgical approach does not affect union of supracondylar femur fractures treated with plate fixation. Poster presented at the 78th Annual Meeting of the American Academy of Orthopaedic Surgeons, February 15-19, 2011,San Diego, CA.

[5] Henderson CE, Lujan TJ, Kuhl LL, Bottlang M, Fitzpatrick DC, Marsh JL: Healing complications are common after locked plating for distal femur fractures. Clin Orthop Relat Res 2011;469(6):1757-1765.

[6] Bottlang M, Feist F. Biomechanics of far cortical locking. J Orthop Trauma. 2011 Feb;25 Suppl 1:S21-8.

[7] Bottlang M, Doornink J, Fitzpatrick DC, Madey SM. Far cortical locking can reduce stiffness of locked plating constructs while retaining construct strength. J Bone Joint Surg Am. 2009 Aug;91(8):1985-94.

[8] Data on file at Zimmer (Liu K et al, ESTABLISHING A STIFFNESS PROFILE, MEASURING AXIAL DISPLACEMENT, AND ESTIMATING AXIAL FATIGUE STRENGTH OF THE 3.5MM ZIMMER MOTIONLOC SCREW FOR PERIARTICULAR LOCKING PLATE SYSTEM IN A PROXIMAL LATERAL TIBIA ZIMMER PERIARTICULAR LOCKING PLATE (ZPLP) BRIDGE PLATING CONSTRUCT, ZRR_WA_2674_13, 24/JUNE/2014)

[9] Bottlang M, Fitzpatrick DC, Sheerin D, Kubiak E, Gellman R, Vande Zandschulp C, Doornink J, Earley K, Madey SM. Dynamic fixation of distal femur fractures using far cortical locking screws: a prospective observational study. J Orthop Trauma. 2014 Apr;28(4):181-8.

[10] Im GI, Tae SK. Distal metaphyseal fractures of tibia: a prospective randomized trial of closed reduction and intramedullary nail versus open reduction and plate and screws fixation. J Trauma. 2005 Nov;59(5):1219-23

[11] Vallier HA, Cureton BA, Patterson BM. Randomized, prospective comparison of plate versus intramedullary nail fixation for distal tibia shaft fractures. J Orthop Trauma. 2011 Dec;25(12):736-41.

[12] Bhandari M, Wasserman SM, Yurgin N, Petrisor B, Sprague S, Dent RE. Development and preliminary validation of a Function IndeX for Trauma (FIX-IT). Can J Surg. 2013 Oct;56(5):E114-20.

[13] Lujan TJ, Madey SM, Fitzpatrick DC, Byrd GD, Sanderson JM, Bottlang M. A computational technique to measure fracture callus in radiographs. J Biomech 2010;43:792-5.

[14] Biswas D, Bible JE, Bohan M, Simpson AK, Whang PG, Grauer JN. Radiation exposure from musculoskeletal computerized tomographic scans. J Bone Joint Surg Am. 2009 Aug. 1;91(8):1882–9.

[15] WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI, Ethical Principles for Medical Research Involving Human Subjects, 60th WMA General Assembly, Fortaleza, Brazil, October 2013

Appendix A: Case Report Forms

Appendix B: Patient Information and Patient Consent