A SINGLE-ARM, OPEN LABEL CLINICAL STUDY TO COLLECT SAFETY DATA ON THE OSTEOPROBE SYSTEM WHEN USED AS A MEASUREMENT TOOL

Protocol Number: *OP2020*

Version: 4.0

Date: 21-SEP-2020

Sponsor:

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REVISION HISTORY

Version	Date	Summary of Changes
1.0	07-MAY-2020	Original Version
2.0	17-JUL-2020	• Update protocol version number and date on **title page**, **footer, Protocol Approval Page** and **Investigator Protocol Signature Page.** • Revise **List of Abbreviations** to add BMSi. • Revise section **1 Study Summary including 1.1 Schedule of Events** to reflect changes made in the body of the protocol and add the name and address of the Investigator and CRO. • Revise section **3.7 Device Traceability** to include detailed information on tip assembly labeling and device accountability. • Revise section **3.8 Supply and Accountability of Investigational Devices** to indicate that device storage instructions are documented in the User Guide. • Revise section **4.0 Benefit-Risk Analysis** to correct the number of peer reviewed articles from 41 to 40. • Revise section **4.2 Risk Mitigation** to correct the name of the product documentation and add a bullet to indicate that subject IDs will be used to mitigate risk. • Revise section **4.3 Anticipated Benefits** to make it clear that there are no anticipated benefits to study subjects • Revise section **4.4 Risk to Benefit Ratio** to indicate that the Investigator will be trained on the protocol. • Revise section **5.2 Secondary Objectives** to indicate that safety events will be characterized. • Revise section **6.1 Study Duration** to specify that AEs will be followed until no further resolution is expected. • Revise section **7.4 Exclusion Criteria** to add clarity to existing exclusions, specify exactly how conditions such as allergies and infections will be determined and documented, specify that only topical antibiotics used at the procedure site are exclusionary, specify that only infections at the procedure site are exclusionary and exclude patients with needle phobia and additional conditions listed in exclusion criteria #14 • Revise section **7.6 Informed Consent** to refer to IRB guidelines. • Revise section **7.8 Screen Failures** to indicate that Screen Failures will be captured on a log and re-screens require sponsor approval. • Revise sections **7.10 Subject Enrollment** and **7.11 Treated Subjects** to clarify when patients are considered enrolled and treated and that treated subjects will be followed for 30 days. • Revise section **8 Study Visit Procedures** to clarify steps and order, list vitals to be captured, allow for screening procedures to be completed over a seven day period, and specify that

		follow ups may be in person or over video (telehealth) with body temperature measurements to help detect possible infections. • Revise section **9 Description of Study Procedures** to clarify how the medical history will be captured, specify the vitals to be captured and document how pregnancy will be evaluated and tested. • Revise section **10.2 Subject Withdrawals** to clarify that patients who withdraw consent prior to treatment will be considered screen failures. • Revise section **14.1 Definitions** to add the definition of a device deficiency and revise the definition of an SAE to match FDA's definition, • Revise section **14.2.2 Relationship** to provide detail on how AE relationship to the investigational device will be determined. • Revise section **14.3 AE Reporting Procedures** to clarify when AE collection begins and requirements for AE reporting, study termination and updating AE status. • Revise section **14.4 Treatment of AEs** to clarify that AEs will be followed until resolved or no further improvement is expected. • Revise section **14.5 Clinical Events Committee** to clarify the role of the CEC. • Revise section **15 Study Monitoring** to include the name and address of the CRO. • Revise section **18 Regulatory Considerations and Ethical Review** to list all accurate regulatory requirements. • Revise section **18.4 Insurance** to clarify who is insured and what they are insured for. • Revise section **19.1 Data Handling and Record Keeping** to clarify roles and responsibilities. • Revise section **19.2 Record Keeping** to include accurate regulatory requirements for retention of study records. • Revise section **19.4 Publication and Data Sharing Policy** to indicate that the study will be registered on clinicaltrials.gov and results posted. • Minor administrative changes involving grammar, wordsmithing, punctuation, page numbers and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment.
3.0	08-SEP-2020	• Revise sections 1, 1.1, 7.4, 8 and 9 to add x-rays for screening and adverse event evaluation. • Revise section 7.9 to clarify that subject IDs are not generated by the investigational device • Revise section 7.10 and 14.3.1 to clarify the point of enrollment
4,0	21-SEP-2020	• Revise section 3.8 to reflect how Tip Assemblies will be tracked. • Make administrative change to footer to fix page numbering • Add section (New section 15) to describe study source documentation

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number: OP2020

Protocol Name: A Single-arm, Open Label Clinical Study to Collect Safety Data on the OsteoProbe System when used as a Measurement Tool

Protocol Version: 4.0

Protocol Date: 21-SEP-2020

This protocol has been read and approved by:

SPONSOR:

Peter Burks CEO Active Life Scientific, Inc.	Date (dd/mmm/yyyy)

CRO:

Iman Ahmad Director, Clinical Affairs MCRA, LLC	Date (dd/mmm/yyyy)
Dave McGurl Director, Regulatory Affairs MCRA, LLC	Date (dd/mmm/yyyy)
Chris Lotter Sr. Director, Data Management & Biostatistics MCRA, LLC	Date (dd/mmm/yyyy)

INVESTIGATOR PROTOCOL SIGNATURE PAGE

I have read and understand this protocol and will conduct the study in accordance with this protocol, all attachments and amendments, applicable Food and Drug Administration regulations, HIPAA, IRB requirements, and the policies of the institutions where the study will take place.

In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Active Life Scientific, Inc. with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

Protocol Number: OP2020

Protocol Title: A Single-arm, Open Label Clinical Study to Collect Safety Data on the OsteoProbe System when used as a Measurement Tool

Protocol Version: 4.0

Protocol Date: 21-SEP-2020

Investigator:

_____

(Print Name)

_____

(Signature) Date (dd/mmm/yyyy)

Upon signing, send a copy of this page to activelife@mcra.com.com and retain a copy for your files.

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
BMSi	Bone Material Strength Index
CDRH	Center for Devices and Radiological Health
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRO	Contract Research Organization
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISF	Investigator Site File
LTFU	Lost to Follow-Up
NRS	Numeric Rating Scale
OHRP	U.S. Office of Human Research Protections
PI	Principal Investigator
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect

1. STUDY SUMMARY

Study Full Title	A Single-arm, Open Label Clinical Study to Collect Safety Data on the OsteoProbe System when used as a Measurement Tool
Study Sponsor	Active Life Scientific, Inc.
Study Number	OP2020
Protocol Date	17-JUL-2020
STUDY OVERVIEW	
Study Design	Prospective, Single Center, Open Label Clinical Study
Purpose	Collect safety data associated with the use of the OsteoProbe System.
Expected Study Duration	The study is expected to take approximately 3 months from first subject enrolled to the last follow-up visit. • 2 months enrollment period (estimation) • 1 month follow-up
Evaluation Schedule	Each subject will be evaluated at: • Screening/Procedure • 1-Day (+2 days) • 7-Day ((±3 days) • 30-Day (±10 days)
ELIGIBILITY CRITERIA	
Intended Subject Population	A total of 40 subjects will be enrolled at 1 site.
Main Inclusion Criteria	In order to be eligible to participate in this study, subjects must meet all of the following inclusion criteria: 1. Be greater than or equal to 22 years of age; 2. Be able to give voluntary, written informed consent to participate and have signed an Informed Consent Form specific to this study 3. If female and of child-bearing potential, must have a negative pregnancy status.
Main Exclusion Criteria	Subjects who meet any of the following criteria will be excluded from participating in this study: 1. Active skin infection at the procedure site as identified during a SOC physical examination. 2. Subject-reported or known systemic infection; 3. Subject-reported or known allergy to local anesthetic; 4. Subject-reported or known allergy to stainless steel or nickel materials; 5. Subject-reported or known current use of systemic antibiotics, or topical antibiotics administered to the procedure site;

	6. Subject-reported or known history of needle phobia; 7. Significant soft tissue at the procedure site which would preclude use of the OsteoProbe in the judgement of the Investigator; 8. Known instance of hardware in the tibia that is intended to be measured based on radiographic imaging; 9. Known instance of a previous or current fracture in the tibia that is intended to be measured based on radiographic imaging; 10. Are known to be actively participating or known to have participated in another clinical investigation for which they received an investigational product (including but not limited to a drug or vaccine) within the last 90 days, or reports that they intend to participate in another clinical investigation during the course of the study; 11. Are known to be currently abusing drugs or alcohol or have a known history of the same within the last 12 months; 12. Have any known or subject reported mental or psychological disorders that, in the judgement of the Investigator, would impair their ability to accurately complete the NRS Pain Score surveys; 13. Are currently a prisoner; 14. Have a condition which, in the judgement of the Investigator, would preclude adequate evaluation of the device's safety and performance. Conditions include but are not limited to: a) Regional or systemic pain syndromes b) Radicular pain syndromes c) Chronic or intermittent leg pain d) Migraine headaches
STUDY ENDPOINTS	
Primary Endpoint	The incidence of device-related serious adverse events (SAEs) in subjects evaluated with the OsteoProbe System.
Secondary Endpoints	The secondary endpoints of this study, following evaluation with the OsteoProbe System, are: 1. NRS Pain scores at Procedure, 1-day, 7-day and 30-day follow up visits; 2. BMSi scores after the OsteoProbe procedure; 3. Adverse event rates through Day 30; 4. Device-related adverse events through Day 30; 5. Serious adverse events through Day 30; and 6. Unanticipated adverse device effects (UADE) through Day 30.
STATISTICAL CONSIDERATIONS	
Sample Size	40 IDE Subjects

	A literature review was performed by the Sponsor who identified six studies with clinically relevant data to serve as an informative prior. These six studies contain 215 subjects with zero subjects experiencing device-related serious adverse events. Given there is no variability between these studies, the data are pooled together and collectively constitute the informative prior. The informative prior was constructed as Jeffries prior plus the data from the literature, that is, Beta(.5 + data, .5 + data). When there are zero device-related SAEs in 40 prospective subjects, the posterior probability will be .9765 and the device will have been shown to meet the performance goal. Therefore, only if there are zero device-related SAE's will the alternative hypothesis be accepted.
Statistical Plan	The primary hypothesis is that the probability of experiencing device-related Serious Adverse Events (SAE) for subjects treated with the investigational device is smaller than the performance goal of 1%. Formally, the hypothesis to be tested is: H_0: The expected proportion of subjects with device-related SAE up to Day 30 (p_T) is greater than or equal to the performance goal (PG) of 1.0%. H_A: The expected proportion of subjects with device-related SAE up to Day 30 (p_T) is less than the performance goal (PG) of 1.0%. These hypotheses may be symbolically represented as: H_0: $p_T \geq PG = 1.0\%$ H_a: $p_T < PG = 1.0\%$ Where p_T is the device-related SAE rate for subjects treated with the investigational device. If the Bayesian Posterior Probability that $p_T < PG$ is greater than or equal to .975, the alternative hypothesis will be accepted, and it will be concluded that the device meets the performance goal.
STUDY MANAGEMENT	
Principal Investigator	Brandon James Essink MD Meridian Clinical Research, LLC, 3319 North 107th Street, Omaha, Nebraska 68134
Clinical Research Organization (CRO)	MCRA, LLC 1050 K Street NW, Suite 1000 Washington DC 20001

1.1 SCHEDULE OF EVENTS

Activity	**Visit 1** Screening/ Procedure[1]	**Visit 2** 1-Day[2,3] (+ 2 days)	**Visit 3** 7-Day[2,3] (±3 days)	**Visit 4** 30-Day[2] (±10 days)	**Unscheduled**
Informed Consent	X	-	-	-	-
Inclusion/Exclusion Criteria Review	X	-	-	-	-
Demographics	X	-	-	-	-
Medical History	X	-	-	-	-
Physical Examination (including vitals)	X	-	-	-	-
X-Rays (AP & Lateral)	X	-	-	-	-
Pregnancy Evaluation/Test[4]	X	-	-	-	-
OsteoProbe Test Procedure	X	-	-	-	-
NRS Pain Score	X[5]	X	X	X	X
Record BMSi Score	X	-	-	-	-
Body Temperature		X	X	X	X
Record/Review Concomitant Medications	X	X	X	X	X
Record/Review Adverse Events	X[6]	X[6]	X[6]	X[6]	X[6]
Record/Review Device Deficiencies	X	-	-	-	-
Work status	X	X	X	X	X

[1] The Screening/Procedure visit may take place over multiple days, but the OsteoProbe procedure must be completed within 7 days of signing the ICF.
[2] To be conducted as telehealth visits with video interviews; option of in-person visits is acceptable if that is preferred by a subject or the Investigator.
[3] Measured from the date of the OsteoProbe procedure.
[4] Female subjects of child-bearing potential only. Negative pregnancy status can be based on self-reported sexual history and contraception use. An in-clinic test must be performed using urine dipstick when the subject thinks there is a potential that they might be pregnant.
[5] The NRS Survey must be completed once prior to the OsteoProbe procedure (baseline) and again following completion of the procedure.
[6] X-rays will be ordered by the Investigator to evaluate any adverse event that may be related to a potential tibial fracture based on clinical exam and/or adverse event details provided by the subject.

2. INTRODUCTION

2.1 BACKGROUND

2.1.1 OsteoProbe® System

The OsteoProbe® System ("OsteoProbe") is a bone microindentation measurement tool.

2.1.2 Diagnosis and Current Treatment Options

The device is a measurement tool that is not intended to make a diagnosis or provide a treatment decision. There are no other available measurement tools for clinical assessment of bone's resistance to microindentation.

3. INVESTIGATIONAL DEVICE

3.1 INVESTIGATIONAL DEVICE OVERVIEW

OsteoProbe is a bone microindentation measurement tool. It is intended to measure bone tissue's resistance to microindentation on the left or right tibia in adults. It is a prescription device per 21 CFR Part 801.109. The device consists of five (5) components: 1) Stylus, 2) Power Controller (Electronics), 3) Holder and Reference Materials, 4) Tip Assembly, and 5) Operator Interface (Figure 1). The OsteoProbe includes a single-use disposable component (Tip Assembly) and reusable components (Stylus, Power Controller, and Holder).

Figure 1: OsteoProbe Device

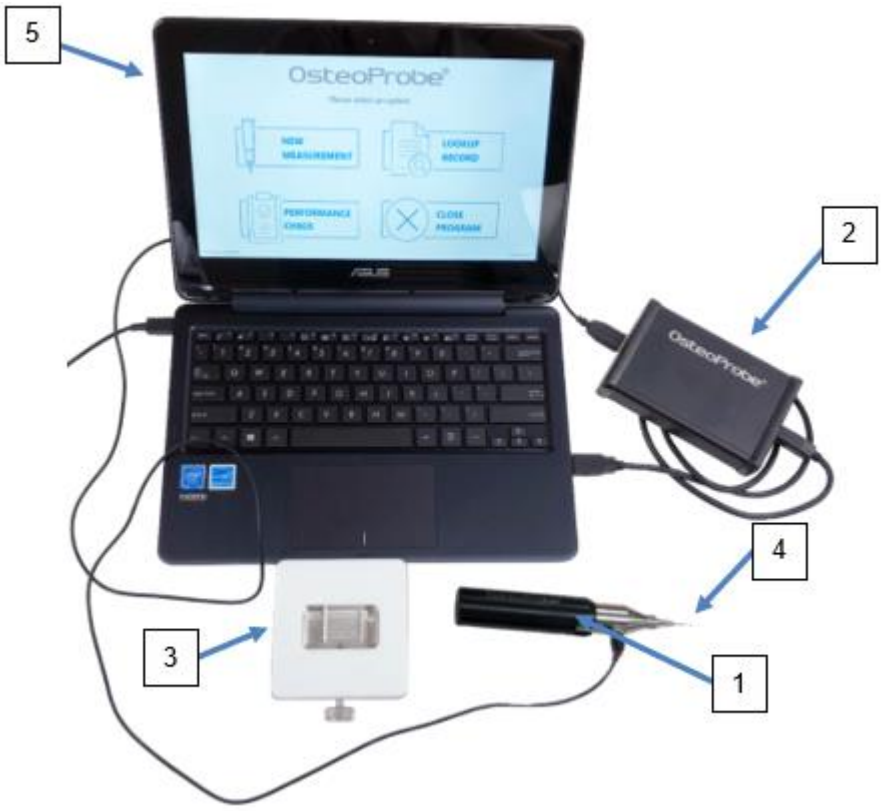


Table 1: OsteoProbe Device Components

Component	Part Number	Component	Representative Image
1	OPA-900	Stylus	
2	OPB-900	Power Controller (Electronics)	
3	OPC-900	Holder and Reference Materials	
4	OPD-900	Tip Assembly	
5	OPH-900	Operator Interface	N/A

3.1.1 Technological Characteristics

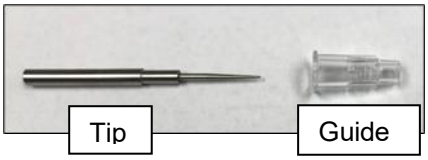
Microindentation is a way of quantifying mechanical properties of materials. There are no devices on the market that can perform microindentation on bone in subjects. Microindentation involves a hard indenter that is pressed into a softer test material (i.e., bone) with a known force. Traditional microindentation testing has specific ASTM defined methods for calculating mechanical properties, like hardness. ASTM defined methods use specific shape indenters and measure indentation depth to calculate an arbitrary hardness number (e.g. Rockwell, Vickers). OsteoProbe operates according to the same principles and calculates a unique parameter: resistance to microindentation. The system software reports a simple numerical score with no reference to clinical utility or other information regarding the health status of the subject.

3.2 OSTEOPROBE DEVICE COMPONENT DESCRIPTION

3.2.1 Tip Assembly

The Tip Assembly is attached to the Stylus in order to perform a measurement. The Tip Assembly is composed of two sub-components, the Tip and a Guide (Figure 2). The Guide retains the Tip and seals via a luer lock fitting to the Stylus. The Tip Assembly is the only component that directly contacts the subject.

Figure 2: OsteoProbe Tip Assembly



The Tip Assembly component is single-use and disposable. The Tip Assembly is packaged and shipped non-sterile. Sterilization instructions are provided to the end user.

3.2.2 Stylus

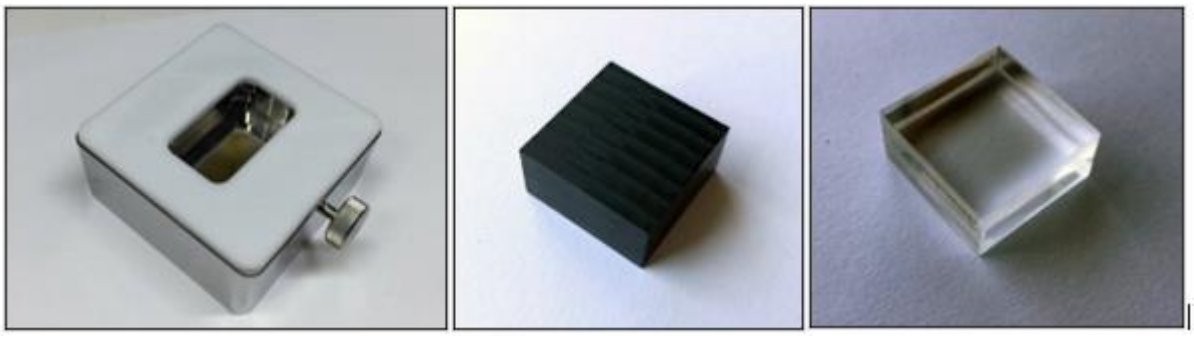
The Stylus component consists of an outer Handle and an internal Body (Figure 3). The Stylus contains an actuation mechanism and sensor that measures the indentation depth of a Tip.

Figure 3: OsteoProbe Stylus

3.2.3 Holder & Reference Materials

The Holder consists of an enclosure/box that secures Reference Materials. There are two Reference Materials. The Reference Block, which is made from polymethylmethacrylate, is used after each measurement on a subject and is discarded after use. The Performance Check Block, which is made from epoxy resin (aka Noryl), is utilized during performance checks. These periodic verifications only ensure system is functioning as expected and are not used to calibrate the device. Both blocks are 1” x 1” x 0.5” (L x W x H) and are disposed of after a single use.

Figure 4: OsteoProbe Holder



Specifications of the OsteoProbe Holder and Reference Materials are summarized in Table 2 below.

Table 2: OsteoProbe Holder and Reference Materials Specifications

Parameter	Value	
Reproducibility	Reference Block: Performance Check Block:	± 1% ± 1%
Dimensions	Reference Block: Performance Check Block: Holder:	1” x 1” x 0.5” 1” x 1” x 0.5” 3.5” x 3.5” x 1.6”
Weight	Holder:	5 lb

3.2.4 Power Controller (Electronics)

The Power Controller consists of electronics that provide power and convert the analog signal from the Stylus into a digital signal which is processed by software on the personal computer terminal. No processing takes place in the power controller.

Figure 5: OsteoProbe Power Controller (Electronics)

Specifications of the OsteoProbe Power Controller are summarized in Table 3 below.

Table 3: OsteoProbe Stylus Specifications

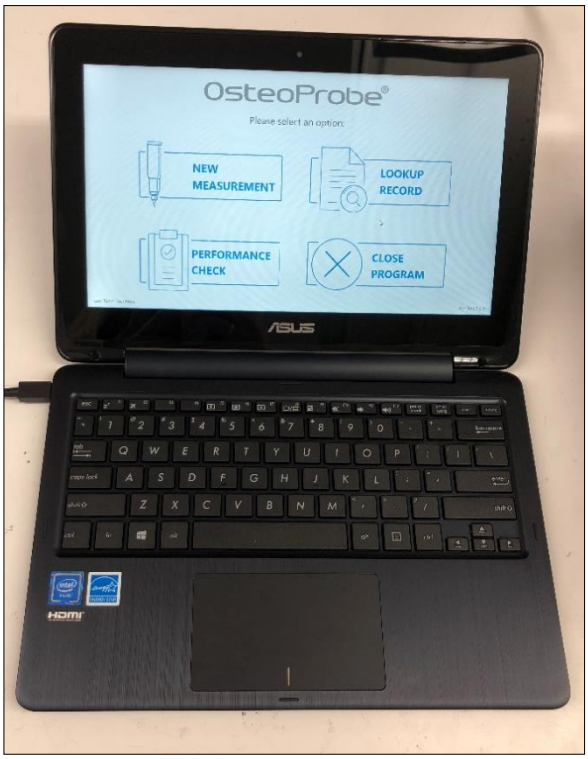
Parameter	Value	
Power Input Requirements	Voltage: Frequency: Current:	100 – 240 V~ 50 – 60 Hz 1.5 A
Case Dimensions	Approximately:	46 x 34 x 17 cm
Case Weight	Approximately:	8 kg
Transport Conditions	Ambient Temperature: Relative Humidity: Atmospheric Pressure:	-20°C to 50°C 10% to 90%, non-condensing 28k Pa to 110 kPa
Operating & Storage Conditions	Ambient Temperature: Relative Humidity: Atmospheric Pressure:	10°C to 30°C 20% to 80%, non-condensing 71 kPa to 101 kPa

3.2.5 Operator Interface

The OsteoProbe Power Controller interfaces with a personal computer terminal via a USB port. The OsteoProbe Operator Interface consists of a software program that runs on a Windows 10 operating system

and processes the digital signal sent by the power controller. The Operator Interface provides the user control of the OsteoProbe to initiate a measurement. The Operator Interface will then store and display the measurement data as a simple numerical score.

Figure 6: OsteoProbe Operator Interface Running on a Laptop



Specifications of the OsteoProbe Operator Interface and Personal Computer specifications are summarized in Table 4 below.

Table 4: OsteoProbe Operator Interface and Personal Computer Specifications

Parameter	Value	
Internet Connectivity	Wireless: Ethernet:	802.11b/g/n RJ-45 (100/1000 Mbps)
Operating System	Windows 10 Professional	
Interface Port	USB A	

3.3 TECHNICAL SPECIFICATIONS

A summary of the system technical specifications is provided below (Table 5).

Table 5: OsteoProbe General Technical Specifications

Parameter	Parameter Value	
System Classification	FDA Class	CAUTION: limited by Federal law to Investigational use only.
	EU Class	Class IIa
Safety Certifications	U.S.A. Certification	IEC 60601-1: 2012
	EU Certification	IEC 60601-1: 2012
EMC Certifications	IEC 60601-1-2:2014, Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance -	

Parameter	Parameter Value
	Collateral standard: Electromagnetic compatibility – Requirements and tests • CISPR 11:2015+A1:2016 - Limits and methods of measurement of radio disturbance, Characteristics of industrial, scientific and medical radio frequency equipment • IEC 61000-4-2:2008 - Electromagnetic Compatibility-Part 4: Testing and measurement techniques – Section 2: Electrostatic discharge immunity test • IEC 61000-4-3:2010 - Electromagnetic Compatibility-Part 4: Testing and measurement techniques – Section 3: Radiated, radio-frequency, electromagnetic field immunity test • IEC 61000-4-4:2012 - Electromagnetic Compatibility-Part 4: Testing and measurement techniques – Section 4: Electrical fast transient/burst immunity test • IEC 61000-4-5:2005 - Electromagnetic Compatibility-Part 4: Testing and measurement techniques – Section 5: Surge immunity test • IEC 61000-4-6:2013 - Electromagnetic Compatibility-Part 4: Testing and measurement techniques – Section 6: Conducted immunity test • IEC 61000-4-8:2009 - Electromagnetic Compatibility-Part 4: Testing and measurement techniques – Section 8: Power frequency magnetic field immunity test • IEC 61000-4-11:2004 - Electromagnetic Compatibility-Part 4: Testing and measurement techniques – Section 11: Voltage dips and interruptions immunity test IEC 61000-3-2:2014 - Electromagnetic compatibility (EMC) -Part 3-2: Limits - Limits for harmonic current emissions (equipment input current < 16A per phase) IEC 61000-3-3:2013 - Electromagnetic compatibility (EMC) -Part 3-3: Limits – Limitation of voltage changes, voltage fluctuations and flicker in public low-voltage supply systems, for equipment with rated current < 16A per phase and not subject to conditional connection
CE Marking	CE Marking for MDD 93/42/EEC

3.4 DEVICE STERILIZATION

The tip is provided non-sterile for end user steam sterilization. All other components are reusable components, have a Spaulding classification of non-critical and must be reprocessed (cleaned and intermediate level disinfected) between each use.

3.5 DEVICE PACKAGING AND LABELING

Device packaging and labeling are described in the User Manual.

3.6 INDICATIONS FOR USE

The OsteoProbe System is indicated for use as a measurement tool to measure bone tissue's resistance to microindentation on the left or right tibia in adults. It is not intended to make a clinical diagnosis.

3.7 DEVICE TRACEABILITY

Each device label includes a unique serial number that is associated with a device history record within the Company quality management system. The Tip Assembly of the device is single-use and disposable. The Tip Assembly components (tip and guide) are not individually serialized. Unique Tip-ID labels are provided which are affixed to each sterilization pouch allowing for accountability of each Tip Assembly and traceability to manufactured lot.

All devices will be shipped via commercial shipper with a tracking number.

3.8 SUPPLY AND ACCOUNTABILITY OF INVESTIGATIONAL DEVICES

Tracking of the investigational product used in this study will be consistent with 21 CFR Part 821 and ISO 14155:2011, and in accordance with local regulations. Devices will be stored in a secure location at the investigational site per the specifications in the User Manual which is only accessible to the Investigator and delegated site staff. OsteoProbe devices, labeled for Investigational Use Only, will be shipped directly to the clinical study site from: *Active Life Scientific, Inc.*

The Investigator or delegate will maintain a Device Accountability Log to document the date of receipt, Tip ID, date of use, and final disposition of each device and Assembly Tip that they utilize during the course of the study. The log will be filed in the site's ISF and will be available for review during monitoring visits.

3.9 DEVICE USE EXPERIENCE AND TRAINING

The study Sponsor will ensure appropriate training for each Investigator prior to initiation of the study at the investigational site. This training will address topics such as the indications and contraindications for the use of the device, device handling, and the procedure.

In addition, the Sponsor will provide training on the protocol, subject eligibility criteria, AE management, post-operative care and follow-up for the Investigator and all delegated site staff.

4. BENEFIT-RISK ANALYSIS

There are 40 peer-reviewed articles that have been published that include discussion of OsteoProbe. Thirty of these 40 publications were clinical studies. None of these published clinical studies were sponsored by the Company. A complete list of published literature can be found in the Report of Prior Investigations.

Active Life Scientific, Inc. has implemented a risk management process in conformance with EN ISO 14971. This risk management process includes risk management plan, risk analysis, risk evaluation, and risk control. The application of this risk management process is documented in a risk management file with a risk management plan. Documentation for the OsteoProbe risk management file will include:

- OsteoProbe device-related risks
- Clinical risks
- Risk mitigation
- Anticipated clinical benefits
- Risk-to-benefit rationale
- Conclusions from pre-clinical risk evaluation and justification for clinical investigation.

4.1 RISKS

The potential device- and procedure-related risks associated with the OsteoProbe device were identified as:

- Allergic reaction to anesthetic or device materials
- Mechanical failure or breakage of device
- Discomfort
- Pain
- Bruising
- Bleeding
- Soft tissue infection
- Bone infection
- Bone fracture

The probability of risks associated with the use of the OsteoProbe device are expected to be low. All adverse events will be captured and assessed by the Investigator.

The subjects in this study will be exposed to the potential risks associated with the OsteoProbe device. There is clinical data on the device which help to understand that the risks associated with participation in the study to be relatively low.

Trial-specific risks include the risks associated with study-related assessments, data collection and loss of confidentiality.

Clinical investigations performed in this trial include non-invasive clinical evaluations and interview questionnaires. Questionnaires applied to this investigation are standard research instruments and have been applied in a large number of studies.

As a result of participating in the study, there could be a risk of loss of protected subject information confidentiality.

4.2 RISK MITIGATION

Appropriate designs and testing have been performed to minimize all risks as far as possible. Clinical monitoring, standard of care, and following the instructions for use ensure risks are minimized. An evaluation of the potential risks associated with use of the OsteoProbe System has been performed to minimize the risks associated with the device. Following are some of the ways in which risks have been or will be minimized.

- Study Design
- Subject monitoring
- Subject selection
- Anonymization of subjects' identities via the use of Subject IDs on all study records
- Device design
- Procedure Guide & User Manual
- Operator training
- Mechanical testing
- Software Validation
- Cybersecurity
- Sterilization and Cleaning Validation
- Electrical Safety and EMC
- Biocompatibility

All subject-associated risks pertaining to the device and procedure have been mitigated or minimized through design, labeling, training and validation/verification according to ISO 14971.

4.3 ANTICIPATED BENEFITS

Although some of the noted risks are potentially significant, they are expected to have low probability of occurrence based on previous device use history. The subject will not directly benefit from the procedure since the device is not therapeutic nor diagnostic. No claims are being made in the trial regarding any potential benefits for the subjects. Since this is an investigational study designed to test the safety of the OsteoProbe®, the potential benefits would be for patients in the future.

4.4 RISK-TO-BENEFIT RATIO

Based on the potential benefits listed above, and the anticipated risks, Active Life Scientific believes this study is justified for the following reasons:

- OsteoProbe device is designed and constructed based on the principles of performing a measurement without causing pain or harm to the subject.
- Robust testing has been performed supporting safety of the OsteoProbe device as designed for its intended use.
- Biocompatibility analyses and material history provide a reasonable assurance of material safety.
- The clinical protocol is designed to yield valid scientific evidence to support an FDA de novo submission.
- The subjects will be screened and closely monitored for any potential adverse events.
- The Investigator has been carefully selected and will be trained on the use of this device and the execution of this clinical protocol.
- Study subjects will be selected according to specific inclusion/exclusion criteria and evaluated frequently.
- The Sponsor will closely monitor the study, and adverse events will be recorded and reported promptly to the Sponsor.
- A Clinical Events Committee (CEC) will be convened to independently review adverse events.

The risks identified above have been minimized to the furthest extent possible, through pre-clinical bench testing, subject and Investigator selection, and proper labeling. In addition, all subjects will be informed of the potential risks during the informed consent discussion.

Therefore, given the information provided throughout this submission, Active Life Scientific has adequately evaluated the safety of the device and put into place adequate clinical controls to initiate the start of an IDE study.

5. STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

Collect and characterize safety data associated with the use of the OsteoProbe System.

5.2 SECONDARY OBJECTIVES

Obtain information on pain regarding the procedure and characterize all safety events.

6. STUDY DESIGN

The study is a prospective, single center, open label clinical study.

6.1 STUDY DURATION

The study is expected to take approximately three (3) months from first subject enrolled to the last follow-up visit.

- 2 month enrollment period (estimation)
- 1 month follow-up

The duration of the study follow-up period was selected to allow sufficient time to identify and assess adverse events that may be related to the use of the investigational device. Subjects who have a adverse event that has not resolved at their 30-day visit will be followed until the event is resolved or no further improvement is expected, or the subject is lost to follow-up.

6.2 TREATMENT/CONTROL GROUP

The study will be a single arm study with no control group.

6.3 PRIMARY ENDPOINTS

The incidence of device-related serious adverse events (SAEs) in subjects evaluated with the OsteoProbe System.

6.4 SECONDARY ENDPOINTS

The secondary endpoints of this study, following evaluation with the OsteoProbe System, are:

1. NRS Pain scores at Procedure, 1-day, 7-day and 30-day follow up visits;
2. BMSi scores after the OsteoProbe procedure;
3. Adverse event rates through Day 30;
4. Device-related adverse events through Day 30;
5. Serious adverse events through Day 30; and
6. Unanticipated adverse device effects (UADE) through Day 30.

6.5 TREATMENT/CONTROL GROUPS AND BLINDING

A total of forty (40) subjects will be enrolled in a single-arm investigational “OsteoProbe” group. In this investigation, neither the Investigator nor the subject can be blinded to the investigation group assignment after undergoing the measurement with the investigational device.

7. SELECTION OF STUDY POPULATION

7.1 SUBJECT RECRUITMENT

Subjects participating in this study will be recruited from the Investigators' standard patient populations. All subjects will be evaluated for study participation based on the inclusion/exclusion criteria listed below. Subjects must meet all of the following inclusion criteria and none of the exclusion criteria. The Investigator maintains exclusive responsibility assessing the eligibility of all potential study participants.

7.2 NUMBER OF SUBJECTS AND INVESTIGATIONAL SITES

A total of forty (40) subjects will be enrolled at a single US site.

7.3 INCLUSION CRITERIA

In order to be eligible to participate in this study, subjects must meet all of the following inclusion criteria:

1. Be greater than or equal to 22 years of age;
2. Be able to give voluntary, written informed consent to participate and have signed an Informed Consent Form specific to this study;
3. If female and of child-bearing potential, must have a negative pregnancy status.

7.4 EXCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from participating in this study:

1. Active skin infection at the procedure site as identified during a SOC physical examination.
2. Subject reported or known systemic infection;
3. Subject reported or known allergy to local anesthetic;
4. Subject reported or known allergy to stainless steel or nickel materials;
5. Subject reported or known current use of systemic antibiotics, or topical antibiotics administered to the procedure site;
6. Subject reported or known history of needle phobia;
7. Significant soft tissue at the procedure site which would preclude use of the OsteoProbe in the judgement of the Investigator;
8. Known instance of hardware in the tibia that is intended to be measured based on radiographic imaging;
9. Known instance of a previous or current fracture in the tibia that is intended to be measured based on radiographic imaging;
10. Are known to be actively participating or known to have participated in another clinical investigation for which they received an investigational product (including but not limited to a drug or vaccine) within the last 90 days, or reports that they intend to participate in another clinical investigation during the course of the study;
11. Are known to be currently abusing drugs or alcohol or have a known history of the same within the last 12 months;
12. Have any known or subject reported mental or psychological disorders that, in the judgement of the Investigator, would impair their ability to accurately complete the NRS Pain Score surveys;
13. Are currently a prisoner;
14. Have a condition which, in the judgement of the Investigator, would preclude adequate evaluation of the device's safety and performance. Conditions include but are not limited to:
    a) Regional or systemic pain syndromes
    b) Radicular pain syndromes
    c) Chronic or intermittent leg pain

d) Migraine headaches

7.5 SCREENING

All subjects will be pre-screened for eligibility based on the inclusion and exclusion criteria described in Sections 7.3 and 7.4. Subjects will be consented prior to initiating any study-specific screening procedures that are not considered routine SOC.

7.6 INFORMED CONSENT

The Principal Investigator or a site representative who is appropriately qualified under national law and who has been trained on the protocol will approach subjects who are potential candidates for participation. They will explain and verify that the subject understands the nature and scope of the study, the procedures to be performed as part of the study, the potential risks and benefits of participation, implications, expected duration, possible treatment alternatives, and follow-up measures if the participation of the subject in the clinical investigation is discontinued; his/her rights; the applicable damage compensation system and will answer any questions that the subject has. The study will be explained to the subject in lay terms and adequate time will be allowed for the subject to ask questions. Interested subjects will be invited to participate in the study and will be asked to provide written informed consent prior to initiation of any study-related procedures. Subjects will be assured that they may withdraw from the study at any time and for any reason, without repercussion. If the subject agrees to participate, the informed consent form (ICF) must be signed and dated by the subject and by the person who obtained informed consent. The informed consent process shall be documented in the subject's medical file.

The informed consent form that is used must be approved by the EC/IRB. A dated and signed copy of the informed consent form will be given to the subject and the original dated and signed consent will be placed in the subject's research file.

If new information becomes available that can significantly affect a subject's future health and medical care that information shall be provided to the subjects affected in written format. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

A signed ICF must be obtained from every subject before any study-related procedures beyond SOC are performed.

Failure to obtain a signed and dated informed consent form prior to performing study-related procedures constitutes a protocol violation, which must be reported to the IRB in accordance with their reporting guidelines.

7.7 SUBJECT ELIGIBILITY

Once written informed consent has been obtained per the procedures outlined in 7.6, the Investigator will proceed to assess whether the subject meets all inclusion and exclusion criteria. The screening process will include, but will not be limited to, a review of the subject's demographics, medical history, physical examination and current medications and therapies.

7.8 SCREEN FAILURES

A screen failure subject is a consented subject that did not have the procedure either due to withdrawing consent or being withdrawn from the study by the Investigator due to not meeting eligibility requirements for treatment.

If a subject signs the ICF but is found ineligible for inclusion in the study prior to or during the procedure, the subject will not be advanced any further in this clinical investigation. The subject's signed ICF and completed inclusion/exclusion criteria will be retained by the Investigator, and the subject will be notified.

Screening data, including the reason for exclusion, will be collected but may not be complete in cases where the subject is determined to be a screen failure early in the screening process. A record of all screened subjects will be maintained in a Screening & Enrollment Log. The subject's exclusion from the study and reason for ineligibility will be documented on the Screening & Enrollment Log.

NOTE: If a subject does not meet the eligibility criteria during their Screening Visit, the subject may be re-evaluated for entry into the study at a later time if deemed appropriate by the Investigator. These subjects will require formal written Sponsor approval, and the subject will need to be re-consented, sign a new informed consent form, and undergo a full review of the inclusion/exclusion criteria by the Investigator.

7.9 SUBJECT IDENTIFICATION

Subjects who consent to participate shall be assigned a unique Subject Identification Number to de-identify their information. This Subject Identification Number will be captured on the Screening & Enrollment Log and used to identify them on all source documents and eCRFs thereafter.

7.10 SUBJECT ENROLLMENT

The point of enrollment occurs when the Investigator delivers the local anesthetic. All enrolled subjects, including those found to be ineligible after consent, will be followed for the next 30 days in accordance with the Schedule of Assessments.

7.11 TREATED SUBJECTS

A treated subject is an enrolled subject who has had the OsteoProbe measurement procedure completed and a BMSi measurement was recorded. All treated subjects, including those found to be ineligible after enrollment, will be followed for the next 30 days in accordance with the Schedule of Assessments.

8. STUDY VISIT PROCEDURES

8.1 VISIT 1: SCREENING/PROCEDURE VISIT

Note: The Screening/Procedure visit may take place over multiple days, but the OsteoProbe procedure must be completed within 7 days of signing the ICF.

Upon successful documentation of informed consent, the subject will be screened to confirm subject eligibility. The screening will include a documentation of demographics, medical history, physical exam with vitals (temperature, blood pressure, pulse and respiratory rate), x-rays to rule out tibial fractures or implants, pregnancy evaluation (for women of childbearing potential only), work status, and concomitant medications.

Upon successful confirmation of subject eligibility, the subject will undergo the following:

Baseline NRS Survey

- The subject will complete a baseline Numerical Rating Scale (NRS) Survey right before initiating the OsteoProbe test procedure

OsteoProbe Test Procedure

- The Investigator will clean the test site and apply a local anesthetic agent prior to performing the OsteoProbe procedure, as outlined in the Procedure Guide, with the assigned device. The Investigator will note the anesthetic agent used, time of delivery and the volume administered in the subject's study records.
- The procedure start time will be recorded as the time of first insertion of the Tip to the bone surface
- The procedure stop time will be recorded as the time the Tip is removed from the skin following the final indentation
- The Investigator will consider the procedure to be successful once the OsteoProbe software displays the BMSi
- If the Investigator cannot complete the procedure for any reason, they should stop the use of the device on this subject and treat the subject per SOC

Post-Procedure (< 60 Minutes)

- The Investigator or delegate will apply a dressing to the test site per SOC
- The Investigator or delegate will record the BMSi Score
- The subject will complete the post-procedure Numerical Rating Scale (NRS) Survey– *this pain survey must be administered prior to performing any adverse event or device deficiency evaluations to prevent information from these assessments biasing the subject's responses.*
- The Investigator or delegate will record adverse events and device deficiencies, if applicable
- The Investigator or delegate will review the suggested post-procedure regimen with the subject per the User Manual
- The Investigator or delegate will perform a review of concomitant medications with the subject

8.2 VISIT 2: 1-DAY FOLLOW-UP (+2 DAYS)

To allow the Investigator's assessment of the subject's progress, the subject will be contacted by the Investigator for a telehealth appointment and interviewed/examined to assess the following:

- The subject's Numerical Rating Scale (NRS) pain score – *this pain survey must be administered prior to performing the other visit assessments to prevent information from these assessments biasing the subject's responses.*
- New or updated adverse events, if applicable
- Current work status
- Review of concomitant medications
- Current body temperature (for telehealth visits, the patient will take their temperature during the visit while being observed and display thermometer reading for the Investigator to confirm and record)

8.3 VISIT 3: 7-DAY FOLLOW-UP (± 3 DAYS)

To allow the Investigator's assessment of the subject's progress, the subject will be contacted by the Investigator for a telehealth appointment and interviewed/examined to assess the following:

- Numerical Rating Scale (NRS) pain score – *this pain survey must be administered prior to performing the other visit assessments to prevent information from these assessments biasing the subject's responses.*
- New or updated adverse events, if applicable
- Current work status
- Review of concomitant medications
- Current body temperature (for telehealth visits, the patient will take their temperature during the visit while being observed and display thermometer reading for the Investigator to confirm and record)

8.4 VISIT 4: 30-DAY FOLLOW-UP (± 10 DAYS)

To allow the Investigator's assessment of the subject's progress, the subject will be contacted by the Investigator for a telehealth appointment and interviewed/examined to assess the following:

- Numerical Rating Scale (NRS) pain score – *this pain survey must be administered prior to performing the other visit assessments to prevent information from these assessments biasing the subject's responses.*
- New or updated adverse events, if applicable
- Current work status
- Review of concomitant medications
- Current body temperature (for telehealth visits, the patient will take their temperature during the visit while being observed and display thermometer reading for the Investigator to confirm and record)

8.5 OUT OF WINDOW AND MISSED VISITS

If a subject fails to participate in a scheduled study visit within the visit window defined in the study protocol but completes the visit prior to the beginning of the next visit window, that visit is considered to have been completed out of window. A protocol deviation must be documented on the appropriate eCRF.

If a subject fails to participate in a scheduled study visit within the visit window defined in the study protocol and the next scheduled study visit window opens, that visit is considered to have been missed. A protocol deviation should be documented on the appropriate eCRF.

All attempts should be made to schedule the subject for the study follow-up as soon as possible so that it is captured late rather than missed completely.

8.6 UNSCHEDULED VISITS

Subjects may be evaluated at unscheduled post-procedure visits by the Investigator or delegated staff as needed. During unscheduled in person or remote visits with the Investigator or delegated staff, the Investigator or delegate will assess the subject's progress and perform/record the following:

- Numerical Rating Scale (NRS) pain score – *this pain survey must be administered prior to performing the other visit assessments to prevent information from these assessments biasing the subject's responses.*

- New or updated adverse events, if applicable. Adverse events must be reviewed and assessed by the Investigator.
- Current work status
- Review of concomitant medications
- Current body temperature (for telehealth visits, the patient will take their temperature during the visit while being observed and display thermometer reading for the Investigator to confirm and record)

8.7 STUDY COMPLETION/DISCONTINUATION

The Primary Endpoints will be evaluated after all subjects reach their 30-Day follow-up visit. Subjects will complete study participation after their 30-Day follow-up visit.

9. DESCRIPTION OF STUDY PROCEDURES

DEMOGRAPHICS
At screening, subject baseline characteristics including, age, gender, BMI, and race/ethnicity will be recorded.

PAST MEDICAL HISTORY
At screening, each subject's medical/surgical history will be reviewed with the subject and updated if needed. Once up to date, this medical/surgical history will be used as the basis for eligibility determination.

PHYSICAL EXAMINATION
A standard physical examination will be conducted according to the site's SOC, and eligibility criteria reviewed to assess subject's suitability for study participation. The physical exam will include a review of vitals (temperature, blood pressure, pulse and respiratory rate).

PREGNANCY EVALUATION & TEST
A pregnancy evaluation will be performed on female subjects of childbearing potential prior to procedure to ensure that the subject is not pregnant. Negative pregnancy status can be based on self-reported sexual history and contraception use. An in-clinic test must be performed using urine dipstick testing when the subject thinks there is a potential that they might be pregnant.

X-RAYS
Subjects will have AP and lateral x-rays collected at the Screening Visit to rule out the possibility of a previous or existing tibial fracture. X-rays will also be ordered by the Investigator to evaluate any adverse event that may be related to a potential tibial fracture based on clinical exam and/or adverse event details provided by the subject.

NUMERICAL RATING SCALE - PAIN
The Numerical Rating Scale (NRS) is a subjective measure in which individuals rate their pain on an eleven-point numerical scale. The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain). It has been shown that a composite scoring system including best, worst, and current level of pain over the last 24 hours was sufficient to pick up changes in pain intensity with maximal reliability.

WORK STATUS

A self-reported work status evaluation will be performed to determine the subject's current work status throughout the trial.

10. EARLY DISCONTINUATION SUBJECTS

10.1 LOST TO FOLLOW-UP (LTFU)

Subjects who miss the final, 30-day study follow-up will be regarded as Lost to Follow-Up. Site staff should perform and document a minimum of three attempts to contact them via phone, and one attempt to reach them via certified mail to bring them in for the final study visit prior to considering the subject LTFU. The staff should document the date and type of attempted communication.

All efforts should be made to have subjects complete all follow-up visits but only subjects that miss the 30-day follow-up will be considered LTFU.

10.2 SUBJECT WITHDRAWALS

Subjects have the right to withdraw from the clinical investigation at any time and for any reason without prejudice to their future medical care by the investigation team or investigational site. The Investigator will ask reason for their withdrawal and will record all information regarding the subject discontinuation. Per Section 7.8, subjects who withdraw consent prior to treatment will be regarded as screen failures.

A Subject may be withdrawn from the clinical investigation for reasons including but not limited to the following:

- Subjects may choose to withdraw from the clinical investigation under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason;
- Any adverse event which, in the opinion of the Investigator, is related to the treatment and will endanger the well-being of the subject if treatment is continued;
- Development of any intercurrent illness(es), infection or condition(s) that might interfere with the clinical investigation;
- Non-compliance with the clinical investigation procedures deemed by the Investigator to be sufficient to cause discontinuation;
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

Regardless of the reason for withdrawal, data available for the subject at the time of withdrawal, including the reason for withdrawal, will be documented in the subject's study records. The Investigator will treat all subjects discontinued from the investigation due to an adverse event until the event resolves. A subject that has been withdrawn from the study after treatment will not be replaced.

10.3 DOCUMENTATION OF EARLY DISCONTINUATION

In every instance where a subject does not complete the study, the Investigator will document the primary reason for discontinuation in the subject's records.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. However, if a subject expresses a desire to withdraw their consent for the study, the site should attempt to obtain written documentation for their study records.

For subjects that are discontinued by the Investigator, the Investigator must notify them of their discontinuation from the study in writing.

10.4 USE OF DATA FROM EARLY DISCONTINUATION CASES

Study data collected previously for subjects who withdraw from the study, are discontinued from the study by the Investigator or LTFU will be included in the data analysis and clinical study report.

10.5 ONGOING TREATMENT FOR EARLY DISCONTINUATION CASES

Subjects who withdraw voluntarily or are discontinued by the Investigator will remain eligible for SOC treatment by the Investigator and study staff.

11. EARLY DISCONTINUATION: STUDY

11.1 PROCEDURE FOR SUSPENSION OR EARLY TERMINATION

The Sponsor may suspend or prematurely terminate this clinical investigation either at the investigational site An Investigator, IRB, or regulatory authority may suspend or prematurely terminate participation in this clinical investigation at the investigational site for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the IRB or regulatory authorities, the Sponsor will suspend the clinical investigation while the risk is assessed. If an unacceptable risk is confirmed, the Sponsor will terminate the clinical investigation.

The Sponsor will consider terminating or temporarily suspending the participation of the investigational site or Investigator if monitoring or auditing identifies serious or repeated deviations on the part of an Investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other party.

If suspension or premature termination occurs:

The Sponsor will remain responsible for providing resources to fulfill the obligations from this protocol and existing agreements for following the subjects enrolled in the clinical investigation, and the Investigator or authorized delegate will promptly inform the enrolled subjects at his/her investigational site.

If the study is terminated, Active Life Scientific, Inc. must comply with all applicable government regulations and the protocol-required subject follow-up. If discontinuation of the study should occur, the Investigator must return all clinical investigation materials (including devices) to the Sponsor, and provide a written statement to the IRB explaining the reasons for the premature termination. All applicable clinical investigation documents shall be subject to the same retention policies, as detailed in Section 19.

11.2 PROCEDURE FOR RESUMING THE CLINICAL INVESTIGATION AFTER TEMPORARY SUSPENSION

When the Sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Sponsor will inform the relevant parties of the rationale and provide them with the relevant data supporting this decision. Concurrence will be obtained from the IRBs and, where appropriate, regulatory authorities before the clinical investigation

resumes. If subjects have been informed of the suspension, the Investigator or authorized delegate will inform them of the reasons for resumption.

11.3 ROUTINE CLOSE-OUT

Routine close-out activities will be conducted to ensure that the Investigator's records are complete, all documents needed for the Sponsor's files are retrieved, remaining clinical investigation materials are disposed of, previously identified issues have been resolved, and all parties are notified.

12. PROTOCOL DEVIATIONS

A protocol deviation is an event whereby the clinical Investigator or site personnel did not conduct the study according to the protocol. Conformance to the protocol is essential to the quality and integrity of the clinical study. Every effort should be made to avoid any deviation from the clinical protocol.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the IRB. Such deviations shall be documented and reported to the Sponsor within 5 days of knowledge. The IRB should be notified of the deviation as required by IRB reporting guidance.

The Sponsor is responsible to assess protocol deviations in an ongoing manner and determine their impact on the conduct of the study. After evaluation of each deviation, the Sponsor will determine if corrective and preventive actions need to occur.

The Sponsor reserves the right to disqualify Investigator on the basis of repeated or serious deviations at their site.

13. CONCOMITANT MEDICATIONS

For the purposes of this clinical study, only current medications being taken or administered for the following will be recorded:

- Pain (any type);
- Inflammation (any type);
- Muscle relaxation;
- Numbness and/or tingling;
- Hormonal replacement therapy; and
- Medications prescribed for treatment of AEs/SAEs

14. ADVERSE EVENT AND DEVICE DEFICIENCY REPORTING

14.1 DEFINITIONS

Device Deficiency (DD) - A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

Adverse Event (AE) – An adverse event is any untoward medical occurrence, disease, injury, or untoward clinical signs (including abnormal laboratory findings, surgical complications, etc.), whether related or unrelated to the investigational device or its use.

Serious Adverse Event (SAE) – A Serious Adverse Event is an AE which:

1. Led to a death,
2. Led to serious deterioration in the health of the subject that either resulted in:
   a) A life-threatening illness or injury, or
   b) A permanent impairment of a body structure or a body function, or
   c) In-patient hospitalization or prolonged hospitalization, or
   d) Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect (not anticipated in this study as pregnant women are excluded from the study).
4. Other Serious (Important Medical Events)

NOTE: Planned hospitalization including for any pre-existing condition, without a serious deterioration in health, is not considered a serious adverse event.

Unanticipated Adverse Device Effect (UADE) – An Unanticipated Adverse Device Effect is:

- Any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death is not previously identified in nature, severity, or degree of incidence in the IDE application; or
- Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subjects.

14.2 CLASSIFICATION OF AN AE

14.2.1 Severity

The Investigator will assess the severity of the AE and classify it according to the following definitions:

MILD: Event/symptom is transient and well-tolerated by the subject.
MODERATE: Event/symptom causes discomfort and interferes with routine activities of the subject.
SEVERE: Event/symptom interferes considerably with the routine activities of the subject or causes inability to work.

These definitions are for descriptive purposes only and are independent of the judgment of whether an event is classified as an AE or an SAE.

14.2.2 Relationship

The relationship between the use of the medical device (including the medical procedure) and the occurrence of each adverse event shall be assessed and categorized. During causality assessment, clinical judgment shall be used, and the Clinical Protocol shall be consulted, as all the foreseeable potential risks are listed here. The presence of confounding factors, such as concomitant medication/treatment, other concurrent illness or risk factors shall also be considered.

The Investigator will assess the potential relationship of the AE or SAE to the use of the investigational device/procedure and classify the causality of the event according to the following definitions.

DEFINITELY RELATED: An AE that has a strong causal relationship. An AE that follows a strong temporal relationship, follows a known response pattern, and cannot reasonably be explained by known characteristics of the subject's clinical state or other therapies.

PROBABLY RELATED: An AE that potentially has a causal relationship. The AE has a reasonable temporal relationship and alternative etiology is less likely compared to the potential relationship to the use of the investigational device/procedure.

POSSIBLY RELATED: An AE that potentially has a causal relationship. The AE has a reasonable temporal relationship to the use of the investigational device/procedure but alternative etiology is equally likely compared to the potential relationship to the use of the investigational device/procedure.

NOT RELATED: An AE without any apparent causal relationship. The AE is due to the underlying disease state or is due to concomitant medication or therapy not related to the use of the investigational device/procedure.

UNKNOWN RELATIONSHIP: If the AE cannot be determined to have a causal relationship, it will be classified as unknown.

NOTE: Where the Investigator or Sponsor remains uncertain about how to classify the event, this should not cause them to exclude any possible relatedness, and the Investigator should consider classifying the event as "Possibly Related".

14.3 AE REPORTING PROCEDURES

14.3.1 AE Reporting

An AE is any undesirable clinical occurrence in a subject (including abnormal laboratory findings) whether or not it is related to the investigational device. Any condition at baseline that is recorded as a preexisting condition is not an AE unless it worsens in intensity or duration.

The collection of AEs will begin in the exam room once the patient is enrolled, i.e. the Investigator delivers the local anesthetic. All AEs that occur through completion of the final follow-up visit for each subject (day 30), whether observed by the Investigator or by the subject, and whether or not thought to be device-related, should be reported in detail and followed to resolution.

The description of the AE will include the date and time of onset, severity, causal relationship to the investigational device, if any treatment was required, and the outcome of the event. Significant new information and updates should continue to be captured in the subject's records and in the EDC as they become available and the adverse event should be followed until it is resolved or no further improvement is expected, or the subject is lost to follow-up.

14.3.2 SAE Reporting

Using the contact information below, the Sponsor should be notified of all SAEs within one (1) business day of the site becoming aware of the event by entering SAE information in the EDC. In the event the EDC is unavailable for any reason, notification to Active Life should be made via email or phone as follows:

Sponsor Contact: Peter Burks
E-mail: peter@activelifescientific.com
Phone: +1-805-770-2600 x106

The Investigator will provide additional information on the SAE by updating the information in the EDC as updates become available. The Sponsor may also ask for additional clinical reports including redacted source documents to be provided by the Investigator to assist in the assessment of the event. Significant new information and updates should continue to be submitted promptly to the Sponsor and entered in the EDC as they become available, and the adverse event should be followed until it is resolved or no further improvement is expected, or the subject is lost to follow-up.

The Sponsor shall ensure that the Investigator submits safety event notifications to the governing IRB within the timeframe specified by the IRB, when applicable. Acceptable means of confirming that the IRB requirements have been met include forwarding a copy of the written, signed report that was sent to the IRB to the Sponsor. Copies of this report should be filed in the Investigator's site files and the Sponsor's Trial Master File.

New SAEs will only be documented for each subject until the last study related subject visit (day 30).

14.3.3 Unanticipated Adverse Device Effect Reporting

The Sponsor shall review all reported SAEs to evaluate whether they meet the criteria for an Unanticipated Adverse Device Effect. For AEs that are determined to be UADEs, the Sponsor will submit an expedited safety report to the FDA's Center for Devices and Radiological Health (CDRH). The expedited safety report will be submitted to the FDA and governing IRB as soon as possible and, in no event, later than **ten (10) business days** after this is determined.

If, following receipt and investigation of follow-up information regarding an AE that was previously determined not to be a UADE, the Sponsor determines that the event does meet the requirements for expedited reporting, the Sponsor will notify the FDA as soon as possible, but in no event later than **ten (10) business days** after this is determined.

14.3.4 Study Termination due to an Unanticipated Adverse Device Effect (UADE)

Active Life Scientific, Inc., in consultation with the Investigators, shall determine if the reported event presents an unreasonable risk to study subjects. If the event is determined to pose an unreasonable risk, the Sponsor may terminate the investigation, or the parts of the investigation presenting that risk, within 5 business days after Sponsor makes an "unreasonable risk" determination or within 15 business days after Active Life Scientific, Inc. first received notice.

14.4 TREATMENT OF AES

The Investigator will ensure that all subjects who experience an adverse event are treated per Standard of Care until the event is resolved or no further clinical improvement is expected, or (if applicable) the subject is LTFU.

14.5 CLINICAL EVENTS COMMITTEE (CEC)

An independent Clinical Events Committee (CEC) comprising of three physicians who are familiar with the study indication will review and adjudicate ***all adverse events and protocol deviations*** to remove Investigator-based bias in AE/PD classification and allow for the poolability of data. The CEC will consist of physician(s) who are not affiliated with the Sponsor and are not participating in the study. The recommendations of the CEC override the Investigator's classification and become part of the clinical trial data set.

The CEC will adjudicate all AEs and potentially reclassify the severity, seriousness, anticipatedness, and relationship to the device/procedure. The CEC will also adjudicate all PDs and potentially reclassify the deviations in terms of whether they are minor or major deviations.

15. SOURCE DOCUMENTATION

The Investigator will be supplied with one physical binder per subject. The binder will contain paper Case Report Forms(CRFs) for collection of study data. It is expected that these CRFs will be the source of all study data. It is possible that additional supplemental source may be captured once the study is underway, but the primary source of all study data is expected to be the paper CRFs.

16. STUDY MONITORING

16.1 SITE MONITORING

The study will be monitored to ensure that it is conducted in conformance with the monitoring plan by an independent CRO to assess continued compliance with the protocol, recognized Good Clinical Practices, FDA's IDE guidance documents, and federal regulations outlined in 21 CFR 812.43(d) and 21 CFR 812.46. In addition, monitoring verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively.

The study may also be subject to a quality assurance audit by the Sponsor or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

The organization responsible for monitoring the study is:

MCRA, LLC
1050 K Street NW, Suite 1000
Washington DC 20001

In addition to ensuring adequate communication between the Investigators and the Sponsor, the CRO's duties may include on-site visits and review of study documents and reported data per the Clinical Monitoring Plan. The CRO study representatives will be provided with appropriate device and protocol training prior to the study and will follow a Monitoring Plan for all study-related monitoring activities.

16.2 MONITORING ACTIVITIES

On-site monitoring visits may include, but are not limited to a pre-study Site Initiation Visit, periodic Interim Monitoring Visits, and a Close-Out Visit at the end of the site's participation in the study.

The Investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to the study-related documents and study-related facilities and has adequate space to conduct the monitoring visit.

Monitoring visits will be documented on monitoring visit reports. On-site and remote monitoring will aim to verify that:

- Compliance with the clinical protocol and applicable regulations is being maintained

- Source data is verified and signed-off upon as accurate
- Subject files are accurate and complete
- Subject withdrawal has been documented (if applicable)
- Subject non-compliance has been documented (if applicable)
- The Investigator and site staff are informed and knowledgeable of all relevant document updates concerning the clinical investigation
- Only authorized individuals are performing study-related functions
- The investigational device is being used according to the protocol and instructions for use
- Adequacy of staffing and facilities
- Signed and dated ICFs have been obtained from each subject
- CRFs and queries are complete
- All adverse events are reported to the Sponsor
- All serious and unanticipated adverse device events are reported to the Sponsor and the IRB
- All other required IRB reports, notifications, applications, submissions, and correspondence are maintained in the Investigator's files and are accurate
- Corrective and preventive actions have been implemented (if applicable)

16.3 FREQUENCY OF VISITS

To ensure that the study is conducted in accordance with the terms of the clinical protocol, study monitors may visit each investigational site throughout the duration of the study per the Clinical Monitoring Plan. The exact frequency of visits shall be determined shall depend upon factors such as but not limited to the following:

- Rate of subject enrollment
- Experience of the Investigator in conducting clinical studies
- Record of previous site compliance

17. AUDITS AND INSPECTIONS

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities. The Investigator must also be prepared to permit study-related audits and inspections by the Sponsor, CRO, IRB and the site's institutional compliance and quality assurance groups. The Investigator will ensure the capability for inspections of applicable study-related facilities, records and reports.

18. STATISTICAL ANALYSIS PLAN

18.1 STUDY HYPOTHESIS

The primary hypothesis is that the probability of experiencing device-related Serious Adverse Events (SAE) for subjects treated with the investigational device is smaller than the performance goal of 1%. Formally, that hypothesis to be tested are:

H_0: The expected proportion of subjects with device-related SAE up to Day 30 (p_T) is greater than or equal to the performance goal (PG) of 1.0%.

H_A: The expected proportion of subjects with device-related SAE up to Day 30 (p_T) is less than the performance goal (PG) of 1.0%.

These hypotheses may be symbolically represented as:

$$H_0: p_T \geq PG = 1.0\%$$

$$H_a: p_T < PG = 1.0\%$$

Where p_T is the device-related SAE rate for subjects treated with the investigational device.

If the Bayesian Posterior Probability that $p_T < PG$ is greater than or equal to .975, the alternative hypothesis will be accepted, and it will be concluded that the device meets the performance goal.

18.2 SAMPLE SIZE ANALYSIS

A review was performed on all the published and unpublished clinical data on the OsteoProbe device. In order to systematically review and identify potential data sources for the informative prior initial criteria was established. In order for the data to be included as an informative prior the following criteria needed to be met:

1. a minimum of 30 days follow-up on patients;
2. the OsteoProbe procedure was administered in a manner consistent with the IDE;
3. the data commented on safety around serious adverse events.

First, a total of 40 published articles were reviewed. Of the published literature, and four published studies met criteria “1” (Patient Follow-up) and “2” (OsteoProbe Procedure) outlined in Section 2, above. The following are the four literature articles:

(1) Sundh D, et al. [JBMR. 2018;33(7):1242-1251],
(2) Pérez-Sáez MJ et al. [Bone. 2018;116:290-294],
(3) Robert Guerri-Fernandez, et al [AIDS 2018, 32:913–920], and
(4) Mellibovsky L, et al. [JBMR 2015;30(9):1651-1656].

However, two (Sundh et al and Pérez-Sáez et al) of the four did not explicitly state the safety outcomes in the study. Given the articles did not explicitly state the safety result, the two articles were excluded from the informative prior. Only two studies met all three criteria, Robert Guerri-Fernandez et al and Mellibovsky L et al.

Table 6. Literature Data Evaluation

Study	Criterion 1: >30 day follow up	Criterion 2: Procedure with OsteoProbe	Criterion 3: Language explicitly	Informative Prior Inclusion

			stating safety results	
Sundh D, et al	X	X		No
Pérez-Sáez MJ et al	X	X		No
Robert Guerri-Fernandez, et al	X	X	X	Yes
Mellibovsky L, et al	X	X	X	Yes

Additionally, a review was performed on all unpublished and ongoing studies with the OsteoProbe device. The same criteria were applied in evaluation of these potential datasets. A total one unpublished or two ongoing studies were found meet the three criteria for inclusion as an informative prior. The table below summarizes the evaluation and inclusion of this information. Each of the included clinical data is further summarized below.

Table 7. Unpublished or Ongoing Clinical Data Evaluation

Study	Criterion 1: >30 day follow up	Criterion 2: Procedure with OsteoProbe	Criterion 3: Language explicitly stating safety results	Informative Prior Inclusion
OHSU (unpublished)	X	X	X	Yes
LUMC (ongoing)	X	X	X	Yes
BARWON (ongoing)	X	X	X	Yes

The summary findings are shown belowTable 8.

Table 8: Informative Prior Data

Study	# Subjects	Device Related SAEs
Robert Guerri-Fernandez (2018)	40	0
Mellibovsky L, et al (2015)	52	0
OHSU	18	0
LUMC (ongoing)	110*	0*
BARWON (ongoing)	50*	0*
Total	**270***	**0***

*Anticipated at the time of De Novo submission

These five studies contain or will contain 270 subjects with an anticipated rate of zero subjects experiencing a device-related Serious adverse events. Given there is no variability between these studies, the data are pooled together and collectively constitute the informative prior. To be conservative, the initial assumption will only consider 215 subjects with zero device-related adverse events. The informative prior was constructed as Jeffries prior plus the data in Table 8, that is, Beta(.5 + data, .5 + data).

When there are zero device-related SAEs in 40 prospective subjects, the posterior probability will be .9765 and the device will have been shown to meet the performance goal. Therefore, only if there are zero device-related SAE's will the alternative hypothesis be accepted.

18.3 STUDY POPULATIONS

18.3.1 Primary Analysis Set

All subjects with a time of procedure start recorded will be included in the Primary Analysis Set. The Primary Analysis Set will be utilized in testing of the primary safety endpoint.

18.3.2 Per Protocol Analysis Set

A per protocol (PP) analysis may be performed excluding enrolled subjects that are subsequently found to not meet the inclusion or exclusion criteria based objective criteria or that experience an intercurrent event during follow-up that makes the device-related SAE endpoint uninterpretable.

18.3.3 Training Cases

There are no training cases for this protocol.

18.4 TESTING OF PRIMARY SAFETY HYPOTHESES

The primary safety hypothesis will be tested by determining the Bayesian posterior probability that the device-related SAE rate is less (i.e., better) than the performance goal. The Bayesian posterior probability will be calculated by updating historical data with prospective trial data. The Bayesian posterior probability will be calculated through numerical integration with regards to the performance goal of .01. When the Bayesian posterior probability of the conditional device-related SAE rate is higher than .975, the alternative hypothesis will be accepted, and it will be concluded that the device has met the specified performance goal of 1%. As stated above, this will only occur when there are zero out of 40 events.

Supporting analyses will summarize the Bayesian posterior probabilities that the device-related SAE rate is lower than varying reference margins.

95% credible intervals of the device-related SAE rate will also be reported without using an informative prior distribution.

18.5 MISSING DATA/SENSITIVITY ANALYSIS

Given the short follow-up, there is not expected to be a large amount of missing data. Detailed descriptions of the reason(s) for missingness will be provided for every missing subject and timepoint. Subjects missing data will be multiply imputed using the posterior distribution of the observed data only. Bayesian posterior summarizes will characterize best- and worst-case scenarios as sensitivity to MAR assumption necessary for the imputation model. There will be no imputation for secondary effectiveness endpoints.

18.6 SECONDARY EFFECTIVENESS ENDPOINTS

The secondary endpoints of this study, following evaluation with the OsteoProbe System, are:

- Follow-up NRS Pain scores take at Procedure, 1-day, and 7-day follow up visits
- BMSi scores at Procedure
- Adverse event through day 30.
- All device-related adverse events through day 30.
- Serious adverse events through day 30; and
- Unanticipated adverse device effects (UADE) through day 30.

Secondary endpoints are described in the Clinical Protocol. Continuous variables will be described by the number of observations, the number of missing observations, means, standard deviations, medians,

minimums, and maximum. Responder variables will be described by the number of observations, the number of missing observations, and percentages. Secondary endpoints may be further described through credible intervals or other posterior distribution summaries.

18.7 SAFETY ANALYSES

Assessment of the safety of the investigational device will include an evaluation of the incidence and severity of complications and adverse reactions associated with the treatment.

Adverse event rates will be summarized by type of AE and for specific AEs in two ways: 1) per subject incidence of specific AEs and classes of AEs and 2) by event, summarizing event counts by visit interval over time and in accordance with FDA Guidance (CDRH 2004).[1] device-related events will be summarized by severity and relatedness.

Event listings that include details such as relatedness, severity, onset, and resolution status will be provided for all events and relevant subsets of events such as serious events and related events. Safety evaluations will be performed using the Primary Analysis Set.

The summary tables will show the adverse events (in coded terms), the total number of events, and the number and the percentage of subjects affected ("subject wise evaluation") and stratified by relation to device or procedure and severity. Data of dropouts will not be presented separately, but possible bias will be discussed in the final report.

All AEs will be summarized in listings for the Primary Analysis Set. The following AE listings will be provided:

1. AE Listing 1 All AEs Sorted by Event Type
2. AE Listing 2 All AEs Sorted by Subject
3. AE Listing 3 Serious AEs
4. AE Listing 4 Severe AEs
5. AE Listing 5 Device-related AEs
6. AE Listing 6 Serious device-related AEs
7. AE Listing 8 Other AEs
8. AE Listing 9 AEs among subjects discontinued early
9. AE Listing 10 AEs among subjects who died

18.8 EVALULATION OF POOLABITIY

Descriptive summarizes of the selected secondary endpoints will be provided stratifying by clinically relevant baseline variables in order to provide evidence that justifies poolability. Clinically relevant baseline variables include:

- Age category (>=50 vs < 50 years old)
- Sex
- Site

18.9 CHANGES TO THE STATISTICAL ANALYSIS PLAN

Any changes to the statistical analysis plan will be fully documented in the Clinical Study Report.

[1] CDRH. Guidance for Industry and FDA Staff: Clinical Data Presentations for Orthopedic Device Applications, December 2, 2004.

18.10 SOFTWARE

All statistical analyses will be performed with SAS version 9.4 or above software (SAS Institute Inc., Cary, North Carolina) or R version 3.6.3 or above (The R Foundation for Statistical Computing Platform).

19. REGULATORY CONSIDERATIONS AND ETHICAL REVIEW

19.1 ETHICAL REVIEW

The clinical investigational plan, informed consent form, any other study specific documents as required by regulations and all amendments to these study documents will be reviewed and approved by the FDA and appropriate IRB, before enrollment of any subject. In addition, the Sponsor will keep the regulatory authorities informed of any UADEs throughout the study course, if applicable.

19.2 REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines and other applicable regulatory requirements including, but not limited to:

- FDA Regulations on Investigational Device Exemption (21 CFR 812)
- FDA Regulations on research with human subjects (21 CFR 50, 54 and 56)
- Health and Human Services (DHHS) Regulations on research with human subjects (45 CFR 46 Subparts A, B, C, and D)
- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry
- The Declaration of Helsinki

19.3 STUDY AMENDMENTS

All changes to this protocol, that impact validity of data, scientific soundness, the rights safety or welfare of the subjects, must be documented in the format of an amendment with justification statements in the cover letter to the IRB and FDA. All amendments must be submitted to the IRB and regulatory authority for review and approval. Following approval, the protocol amendment will be distributed to all protocol recipients at the investigational site.

19.4 INSURANCE

The Sponsor will have clinical trial insurance in place during the study, with appropriate coverage for the duration of the entire study. Subjects who participate in this study will be insured against study-related injury according to local regulation requirements.

20. DATA HANDLING AND RECORDKEEPING

20.1 DATA MANAGEMENT

All required data for this study will be collected on standardized eCRFs. The Investigator or investigational site will maintain, at the investigational site, in original format, all essential study documents and source documentation that support the data collected on the study subjects in compliance with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and any local regulatory guidelines.

eCRFs will be completed in a 21 CFR Part 11 compliant electronic data capture (EDC) system for each subject enrolled into the clinical study. The Investigator or delegated site staff will enter the source data into the eCRFs and study monitors will perform a source document verification process.

The Investigator will be responsible for the review and sign off on the Eligibility Criteria, Adverse Event, Protocol Deviation and Study Completion eCRFs and will sign each subject's casebook once the subject completes the study to attest that all data entered on the eCRFs are complete and accurate. All of the above signatures will be completed digitally within the EDC system using the system's Part 11 compliant digital signature system function.

Any required data clarifications will be handled within the EDC system's query management system. The EDC will be programmed to automatically place data clarification queries on missing values and values out of acceptable ranges. Study monitors and data managers will also be able to add data clarification queries to data points within the system. Study coordinators will have the opportunity to correct data and/or respond to the query for review by monitors and data managers.

All procedures for the handling and analysis of data will be conducted using good clinical data management practices within systems meeting FDA guidelines for the handling, storage, and analysis of data for clinical studies.

The CRO study representatives will follow a Data Management Plan for all study-related data management activities.

20.2 RECORD KEEPING

The Investigator and the Sponsor will maintain accurate, complete, and current records relating to participation in this clinical investigation. If the Investigator wishes to assign the responsibility of maintaining the study files to someone else or move them to another location, he/she should consult with the study sponsor in writing regarding the change. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and the Sponsor must receive written notification of this custodial change.

The sponsor and Investigators will retain the specified records and reports for up to two years after the marketing application is approved for the investigational device; or, if a marketing application is not submitted or approved for the investigational device, until two years after investigations under the IDE have been discontinued and the FDA so notified.

The Investigator and Sponsor will maintain records in accordance with 21 CFR 812, Subpart G, to include:

- Current and past versions of the IRB-approved clinical protocol and amendments and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- FDA correspondence related to the IDE application; including supplemental IDE applications, current Investigator lists, progress reports
- IRB correspondence (including submissions and approval notifications) including safety and protocol deviation reports, and annual or interim reports
- Signed Clinical Trial Agreement

- Signed Investigator Agreements and financial disclosure forms for the participating Investigator
- Curriculum vitae (Investigator and Sub-Investigators)
- Certificates of required training for the Investigator and any Sub-Investigators, including human subject protection and Good Clinical Practice
- Instructions for handling the investigational device and other study-related materials
- Device tracking logs
- Signed ICFs
- eCRF and Source Documents
- Monitoring visit confirmation and follow-up letters
- Copies of relevant Sponsor-Investigator correspondence, including notifications of adverse event information
- Screening and Enrollment Log
- Signed informed consent forms
- Final clinical study report

20.3 DATA PROTECTION AND SUBJECT CONFIDENTIALITY

Subject confidentiality will be maintained throughout the study in a way that ensures that data can always be tracked back to the source data. For this purpose, a unique subject identification code (two digit site identification number and three digit subject name identification number code assigned sequentially) will be used that allows identification of all data reported for each subject without traceability back to the actual subject.

The Investigator shall provide direct access to source data during and after the clinical investigation for monitoring, auditing, IRB review and regulatory authority inspections.

“Protected Health Information” will be treated and maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy rule.

The duration of storage time of personal data at the investigational site will be in accordance with national regulations (see section 19.2).

Information obtained in the course of executing this study may be presented for regulatory, clinical or educational purposes as long as no subject is identified. The data collected is the property of Active Life Scientific, Inc.

20.4 PUBLICATION AND DATA SHARING POLICY

Data generated from the conduct of this study is intended be used to support an application by Active Life Scientific, Inc. as a de novo submission for FDA. Publication of the results of the study will follow Active Life Scientific, Inc.’s Publication and Presentation Policy.

The study will be registered on Clinicaltrials.gov in compliance with 42 CFR Part 11. Results of the study, including an unanticipated early termination of the study, will be posted to the Clinicaltrials.gov database at

the conclusion of the study. In the event that the study is terminated early, the posting of these results will be completed within 30 days of completion of data analysis.

20.5 INVESTIGATOR REPORTS

The Investigator is responsible for the timely preparation and submission of the reports cited below.

Table 9: Investigator Reports

Report	Sent To	Timing of Report
Unanticipated adverse device effect (UADE)	Active Life Scientific, IRB	UADE must be reported as soon as possible, but in no event later than 10 business days after the Investigator first learns of the event
Withdrawal of IRB approval	Active Life Scientific	Reported within 5 business days
Progress reports	Active Life Scientific, IRB	Reported as requested by Active Life Scientific or the reviewing IRB, but at least yearly
Deviations from the investigational plan	Active Life Scientific, IRB (FDA)	A deviation to protect the life or physical well-being of a subject in an emergency must be reported as soon as possible but no later than 5 business days after the emergency occurred. Deviations that may affect the scientific soundness of the investigational plan or the rights, safety, or welfare of the subject (and are not an emergency) must receive prior approval by Active Life Scientific and be reported to the FDA and IRBs.
Device use without informed consent	Active Life Scientific, IRB	This deviation must be reported within 5 business days after the use occurs.
Final Report	Active Life Scientific, IRB	This report must be submitted within 3 months after termination or completion of the investigation or the Investigator's part of the investigation.
Other	FDA, IRB	Upon request, accurate, complete, and current information about any aspect of the investigation must be reported.