Prospective, Multi-Center, Randomized Study to Evaluate the OrthoCor Active System for Pain Relief

Investigational Product:	**OrthoCor Active System**
Protocol Number:	**OCM-OAS-01 Version 3.0**
Date:	**07September2022**
ClinicalTrials.gov Number:	**NCT05244187**

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Medical, Clinical and Operational Support

Sponsor Name:	Caerus Corporation
Sponsor Telephone Number	+1 651-440-9345
Manufacturer and Sponsor Address:	Caerus Corporation 12251 Red Fox Road Arden Hills, MN 55112

1.2 Protocol Administrative Information

Protocol Number:	OCM-OAS-01
Revision Number:	Version 3.0
Protocol Date:	07-Sep-2022
Investigational Product:	OrthoCor Active System

1.3 Amendment History:

Date	Amendment Number	Amendment Type
30-Nov-2021	Original	Original protocol, version 1.0
18-Jan-2022	1	Amended protocol, version 2.0
07-Sep-2022	2	Amended protocol, version 3.0

1.4 Sponsor Protocol Approval

Representatives of Caerus Corporation.

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6 (ICH GCP E6).

All applicable laws and regulations, including, without limitation, data privacy laws and regulations.

SIGNATURES

Kai Kroll, Caerus CEO or Designee	Date
David Rothkopf, MEDIcept Regulatory Affairs	Date
Steven Walfish, MEDIcept Biostatistician	Date
Adelina Paunescu, MEDIcept Clinical Operations	Date

INVESTIGATOR AGREEMENT

I will provide copies of the clinical trial protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure they are fully informed regarding the investigational products and the conduct of the study.

I will obtain written informed consent from all participating subjects/patients in accordance with requirements as specified in ICH Guideline for Good Clinical Practice; Section 4.8 and I will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board (IRB). I will use only the informed consent form approved by the Sponsor and the IRB or its representative.

I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee and that all administrative requirements of the governing body of the institution will be complied with fully.

I also agree to report all information or data in accordance with the protocol and I agree to report without unjustified delay, all Adverse Events (AEs) and Serious Adverse Events (SAEs) that could have led to any Unanticipated Adverse Device Events (UADEs).

I further agree that Caerus Corporation and/or designee will have access to any original source documents from which electronic or paper case report form (CRF) information may have been generated.

I also agree to have control over all clinical supplies (including investigational products) provided by Caerus Corp. and/or designee and collect and handle all clinical specimens in accordance with the protocol. I further agree not to originate or use the name of Caerus Corp., OrthoCor Medical and/or OrthoCor Active System, or any of its employees, in any publicity, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this protocol, to any amendment hereto, or to the performance hereunder, without the prior written consent of Caerus Corporation.

I herewith declare that I agree with the protocol described in detail in this document and agree to conduct the study in accordance with the protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

Investigator Name (print) _____

Investigator Signature _____ Date _____

Name of Facility _____

Location of Facility (City) _____

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2.0 PROTOCOL SYNOPSIS

Sponsor	Caerus Corporation
Protocol Title:	Prospective, Multi-Center, Randomized Study to Evaluate the OrthoCor Active System for Pain Relief
Protocol Number	OCM-OAS-01
Investigational Device:	OrthoCor Active System
Device Description:	The OrthoCor Active System is a portable (battery operated) non-invasive device that delivers Pulsed Electromagnetic Field (PEMF) therapy for General Use of temporary pain relief, utilizing wraps that position the therapy, such as on the ankle, back, knee, wrist, elbow, shoulder, foot, or neck. The microchip delivers the pulsed RF signal to the tissue target via the inductive coupling with an applicator coil. The system also uses disposable, single-use, air activated OrthoPods that provide heat.
Study Objective:	The objective of this study is to evaluate the OrthoCor Active System in individuals prescribed its use in comparison with Standard of Care (SOC) intervention. Pain assessments will be conducted utilizing the Mankoski Pain Scale.
Study Design:	Prospective, Multi-Center, Randomized, Open Label Study.
Subject Population:	Both males and females, presenting to the designated study sites with pain in superficial soft tissue, such as in the ankle, back, knee, wrist, elbow, shoulder, foot, or neck who are prescribed the use of the OrthoCor Active System or Standard of Care (SOC) intervention.
Rationale:	According to the Centers for Disease Control and Prevention, 50 million adults in the United States have chronic daily pain, with 19.6 million adults experiencing high impact chronic pain that interferes with daily life or work activities. Clinical best practices may recommend a collaborative, multimodal, multidisciplinary, patient-centered approach to treatment for various acute and chronic pain conditions to achieve optimal patient outcomes. For improved functionality, activities of daily living, and quality of life, clinicians are encouraged to consider and prioritize, when clinically indicated, nonpharmacologic approaches to pain management. An alternative treatment option can be the use of restorative therapies. Restorative therapies play a significant role in acute and chronic pain management, and positive clinical outcomes are more likely if restorative therapy is part of a multidisciplinary treatment plan following a comprehensive assessment. Patient outcomes related to restorative and physical therapies tend to emphasize

	improvement in outcomes, but there is value in restorative therapies to help maintain functionality. The Orthocor Active System delivers OrthoCor's patented Pulsed Electromagnetic Field (PEMF) therapy, a noninvasive, temporary relief for pain. The key to OrthoCor's therapy is the use of specialized PEMF technology. In particular, PEMF works at the source of injuries, and helps accelerate the body's natural anti-inflammatory and recovery responses. Inside every Active System is the OrthoCor, a microchip that delivers PEMF directly to the source of injuries. Furthermore, PEMF has been shown to stimulate reaction pathways that result in pain and inflammation reduction.
Study Assessment/ Evaluation:	Pain assessments will be conducted utilizing the Mankoski Pain Scale which will be compared to the pain assessments of subjects who were prescribed the Standard of Care (SOC) intervention.
Study Endpoints:	Primary Safety Endpoint: The safety endpoint of this study will be the adverse events reported with the OrthoCor Active System pain after 2 weeks of use. Primary Efficacy Endpoint: The efficacy endpoint of this study will be the comparison of the OrthoCor Active System pain assessment scores to the Standard of Care (SOC) intervention after 2 weeks of use.
Exploratory Assessment:	Exploratory Assessment: The exploratory assessment of this study will be the performance of the OrthoCor Active System after an additional 2 weeks of use and is intended for research and publication only.
Number of Patients:	Up to 100 subjects will be enrolled in order to achieve up to 50 using the OrthoCor Active System and up to 50 using the Standard of Care (SOC) intervention. The patients will be enrolled consecutively at the participant site until enrollment is met. For the exploratory assessments, the 50 subjects who received SOC will have the opportunity to cross-over and use the OrthoCor Active system.
Number of Sites:	Five (5) sites are anticipated
Anticipated Study Duration:	3-5 months
Study Eligibility Criteria	Inclusion Criteria: Participants must meet ALL of the following: 1. Individuals presenting with pain in superficial soft tissue, such as ankle, back, knee, wrist, elbow, shoulder, foot, or neck pain,

	or minor muscular and joint aches and pains associated with over exertion, strains, sprains, or arthritis 2. Prescribed use of the OrthoCor Active System or Standard of Care (SOC) intervention 3. Willing and able to provide informed consent or obtain consent from legal authorized representative (LAR) Exclusion Criteria: Participants must not meet ANY of the following: 1. Have a cardiac pacemaker, cardioverter defibrillator, neurostimulator, infusion pump or any active medical implant 2. Have an implanted metallic lead or any type of wire coil implant, or any implanted system that may contain lead 3. Current or expected use of opioids 4. Who are or may be pregnant 5. Have an open wound at the area of application 6. Are not capable or fully aware to the sensation of heat 7. Have poor circulation or heart disease 8. Have diabetes 9. Under the age of 18 or individuals with open bone growth plates 10. Unable to provide consent or obtain consent from a LAR 11. Unwilling or unable to use the OrthoCor Active System or Standard of Care (SOC) intervention 12. Unwilling or unable to complete the daily pain assessment 13. Enrolled in a study to evaluate an investigational drug 14. Prisoner or under incarceration
Statistical Analysis	Primary efficacy analyses The primary effectiveness endpoint of this study is the change from baseline of the OrthoCor Active System compared to the Standard of Care (SOC) intervention.

3.0 LIST OF ABBREVIATIONS

Abbreviation	Definitions
AE	Adverse Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations, Medical Sciences
CRF / eCRF	Case Report Form/ Electronic Case Report Form
CRO	Contract Research Organization
EDC	Electronic Data Capture
eDiary	Electronic Diary
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFU	Instructions For Use
IRB	Institutional Review Board
LAR	Legal Authorized Representative
PD	Protocol Deviation
PEMF	Pulsed Electromagnetic Field
PI	Principal Investigator
POC	Point of Care
RF	Radio Frequency
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SD	Standard Deviation
SDV	Source Data Verification
SID	Subject Identification Number
SOC	Standard of Care
UADE	Unanticipated Adverse Device Effect
WOCBP	Women of Child Bearing Potential

4.0 INTRODUCTION

4.1. Background and Significance

According to the Centers for Disease Control and Prevention, 50 million adults in the United States have chronic daily pain, with 19.6 million adults experiencing high impact chronic pain that interferes with daily life or work activities. Clinical best practices may recommend a collaborative, multimodal, multidisciplinary, patient-centered approach to treatment for various acute and chronic pain conditions to achieve optimal patient outcomes. For improved functionality, activities of daily living, and quality of life, clinicians are encouraged to consider and prioritize, when clinically indicated, nonpharmacologic approaches to pain management.[1]

An alternative treatment option can be the use of restorative therapies. Restorative therapies play a significant role in acute and chronic pain management, and positive clinical outcomes are more likely if restorative therapy is part of a multidisciplinary treatment plan following a comprehensive assessment.[1]

The OrthoCor Active System uses specialized Pulsed Electromagnetic Field (PEMF) technology to relieve pain and reduce edema through safe, clinically proven therapy. PEMF is a low-level, time-varying electromagnetic field that penetrates superficial soft tissue, helping to accelerate the body's natural anti-inflammatory and recovery responses. Inside every OrthoCor Active System is proprietary electronic circuitry that delivers PEMF to the source of injuries. PEMF has been shown to stimulate reaction pathways that result in pain and inflammation reduction. OrthoCor's patented PEMF accelerates the binding of calcium (Ca2+) to calmodulin (CaM), the process responsible for the body's natural, anti-inflammatory nitric oxide (NO) cascade [2-5]. NO is a key element in the body's natural healing process. It is also a vasodilator, increasing blood and lymphatic flow.[3] Additionally, NO down-regulates interleukin-1 beta (IL1β) and inducible nitric oxide synthase (iNOS), which leads to reduced cyclooxygenase-2 (COX-2) and prostaglandins – molecules responsible for causing inflammation and pain [2-5]. Unlike other systemic COX-2 inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs), OrthoCor's targeted PEMF signals stimulate localized reaction pathways, thereby reducing pain and inflammation without the risks and side effects associated with NSAIDs[2-5].

4.2. Previous Experience

In previous clinical studies, OrthoCor Active System was clinically proven to reduce pain, swelling and provide lasting relief without the use of pain medications or invasive procedures.

OrthoCor Medical Inc. conducted a prospective, double blind, placebo controlled, randomized pilot study (2014-2016), enrolling 80 patients with Kellgren-Lawrence knee arthritis who used the OrthoCor knee system, which showed a significant 60% reduction in the mean pain score within the first 3 days of use compared with the sham group [2].

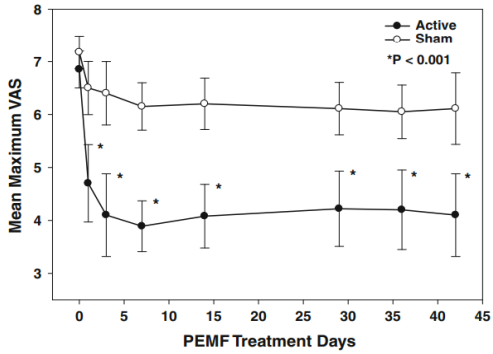

Fig. 3 Effect of a radio frequency PEMF signal, configured, a priori, to target the CaM/NO/cGMP signaling pathway, on pain from early stage knee OA. This is a repeated measures intra-cohort comparison which shows this signal caused a nearly 60 % reduction in mean VAS pain scores within the first 3 days for the active cohort, which persisted to day 42 for all enrolled active patients. There was no significant difference in mean VAS scores for the sham cohort at any time point, or in mean baseline VAS scores for the active and sham cohorts

A preliminary study[6] conducted by OrthoCor Medical Inc. in 33 patients suffering from knee osteoarthritis utilizing the OrthCor knee system, showed reduced pain and stiffness after 15 days of treatment with a 43% reduction in pain score (Figure 3) and a 79% improvement in activity limitations, symptoms, emotions, and overall quality of life (Figure 2).

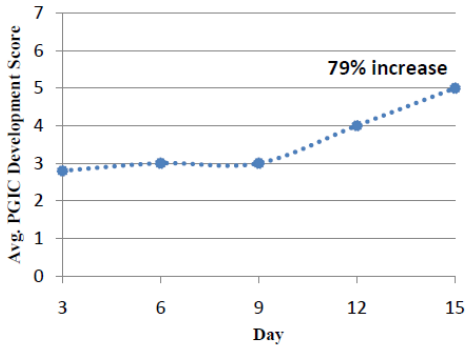

Figure 2. Average score for level of improvement portion of PGIC questionnaire. The results show a 79% improvement in development after 15 days of therapy.

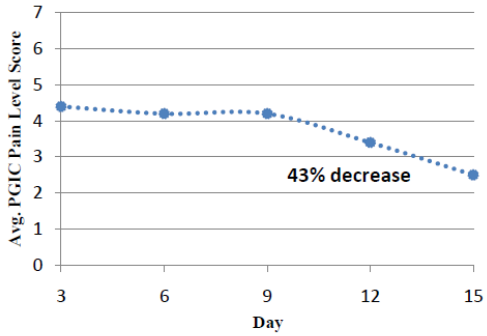

Figure 3. Average score for pain level portion of PGIC questionnaire. A score of 10 indicates a maximum increase in pain. The results show that pain level has decreased 43% following 15 days of therapy.

4.3. Name and Intended Use

The OrthoCor Active System is a portable (battery operated) non-invasive shortwave diathermy medical device which applies electromagnetic energy at a radio frequency (RF) of 27.12 MHz for the treatment of pain in superficial soft tissue, such as in the ankle, back, knee, wrist, elbow, shoulder, foot, or neck. The OrthoCor Active System delivers the pulsed RF signal of 6.5+0.5 Ws/cm^3 to the tissue target via the inductive coupling with an applicator coil. The system also uses disposable, single-use, air activated OrthoPods that provide heat for the temporary relief of minor muscular & joint aches & pains associated with over-exertion, strains, sprains, and arthritis.

4.4. Indication for Use

The OrthoCor Active System is indicated for adjunctive use in the treatment of pain, and temporary relief of minor muscular and joint aches and pains associated with over-exertion, strains, sprains, and arthritis.

5.0 STUDY RATIONALE

The objective of this study is to evaluate the OrthoCor Active System in individuals presenting with post-operative pain and edema in superficial soft tissue. The OrthoCor Active System will be compared to the SOC intervention.

6.0 DEVICE DESCRIPTION

The OrthoCor Active System includes the following components:

Multi-Use

- The Active System can be used in multiple body locations, some examples are shown below

Figure 1. OrthoCor Active System Multi-Use (Not to scale).

The OrthoCor Active system has PEMF and heat as the active components as provided by the 2 OrthoPods inserted in the body specific wraps for the purpose of holding them in place.

The OrthoPods are the same for all body location configurations and only the wrap is modified for the purpose of holding them in the treated area.

Figure 2. Image shows the Use of OrthoCor Active Ankle System (Not to scale).

Figure 3. Image shows the Use of OrthoCor Active Back System (Not to scale).

Figure 4. Image shows the Use of OrthoCor Active Knee System (Not to scale).

Figure 5. Image shows the Use of OrthoCor Active Wrist System (Not to scale).

Figure 6. Image shows the Use of OrthoCor Active Elbow System (Not to scale).

Figure 7. Image shows the Use of OrthoCor Active Shoulder System (Not to scale).

Figure 8. Image shows the Use of OrthoCor Active Neck System (Not to scale).

Single-Use

- OrthoPods

Instructions for Use manual is provided to the patient with the product (see Appendix A).

7.0 STUDY OBJECTIVES and ENDPOINTS

The primary objectives are to compare the pain assessment scores of the SOC intervention to the OrthoCor Active System pain assessment scores.

The primary effectiveness endpoint of this study is the change from baseline of the OrthoCor Active System compared to the SOC intervention.

8.0 STUDY DESIGN

8.1 Study Details

This is a prospective, multi-center, randomized, open label study that will enroll up to 100 subjects.

8.2 Number of Clinical Sites

The trial will be conducted in up to five (5) participating sites in the USA.

8.3 Subject Population

The target population for this measurement consists of both males and females, presenting to the designated study sites with pain in superficial soft tissue, such as in the ankle, back, knee, wrist, elbow, shoulder, foot, or neck who are prescribed the use of the OrthoCor Active System or Standard of Care (SOC) intervention.

Eligible subjects must meet the inclusion and exclusion criteria described in Sections 8.4 and 8.5. Any questions from the investigative site regarding a potential subject's eligibility for enrollment must be discussed with the Sponsor (or designee) prior to consenting and enrolling the subject into the study for the investigational measurement.

It is estimated that up to 100 subjects may be enrolled into the study.

Patients will be enrolled consecutively at each participant site until up to 50 using the OrthoCor Active System and up to 50 using the Standard of Care (SOC) intervention have enrolled. The CRO will stratify the arms (OrthoCor Active System vs SOC) by selecting the arm alternatively. The patients will be enrolled consecutively at the participant site until enrollment is met.

As part of exploratory research extension, patients using the OrthoCor Active system will have the opportunity to continue on the trial for an additional 2 weeks. Participants assigned SOC have the opportunity to cross-over using the OrthoCor Active system for the additional 2 weeks. Participation in the exploratory extension is optional.

8.4 Inclusion Criteria

Participants must meet ALL of the following criteria:

1. Individuals presenting with pain in superficial soft tissue, such as ankle, back, knee, wrist, elbow, shoulder, foot, or neck pain, or minor muscular and joint aches and pains associated with over exertion, strains, sprains, or arthritis
2. Prescribed use of the OrthoCor Active System or Standard of Care (SOC) intervention
3. Willing and able to provide informed consent or obtain consent from legal authorized representative (LAR)

8.5 Exclusion Criteria

Participants must not meet ANY of the following criteria:

1. Have a cardiac pacemaker, cardioverter defibrillator, neurostimulator, infusion pump or any active medical implant
2. Have an implanted metallic lead or any type of wire coil implant, or any implanted system that may contain lead
3. Current or expected use of opioids
4. Who are or may be pregnant
5. Have an open wound at the area of application
6. Are not capable or fully aware to the sensation of heat
7. Have poor circulation or heart disease
8. Have diabetes
9. Under the age of 18 or individuals with open bone growth plates
10. Unable to provide consent or obtain consent from a LAR
11. Unwilling or unable to use the OrthoCor Active System or Standard of Care (SOC) intervention
12. Unwilling or unable to complete the daily pain assessment
13. Enrolled in a study to evaluate an investigational drug
14. Prisoner or under incarceration

9.0 SUBJECT PARTICIPATION AND STUDY DURATION

Potential study subjects are males and females presenting to the designated study sites with pain in superficial soft tissue, such as in the ankle, back, knee, wrist, elbow, shoulder, foot, or neck who are prescribed the use of the OrthoCor Active System or Standard of Care (SOC) intervention. This will be a one-time on-site visit with data collection for 14 days.

All study participants will have the opportunity to continue in the research extension with data collection for another 14 days. Participation in the exploratory extension is optional.

9.1 Site selection Criteria

The trial will be conducted at up to five (5) sites. The sites will be selected by the CRO and agreed upon by the Sponsor.

- The institution/collection site must have access to the necessary equipment and supplies that are needed for the study and for study data collection.
- Clinical research study experience and resources that demonstrate good compliance with study requirements and timely, complete documentation of subject visits.
- Investigative team should designate a study coordinator to manage the study.
- Ability to adhere to the standards of Good Clinical Practice (GCP) and ICH E6(R2).
- Agree to comply with data collection requirements and data entry timelines.
- Study site will respond to queries from CRO, Caerus Corporation (or designee) in a timely manner.
- Willingness to allow personnel from CRO, Caerus Corporation (or designee) access to, Investigator's study records, data, and subject files as they pertain to the study.

9.2 Screening Process

Subjects will be prescreened for eligibility and if qualified will be approached with the study information and asked if they are willing to participate.

Informed consent will be obtained per section 14.2. All patients who sign a consent form are considered study subjects. A study participant is considered enrolled after they have signed an informed consent form and after the inclusion/exclusion criteria have been met.

After an IRB approved Informed Consent Form is obtained and study inclusion/exclusion criteria are met, the study assessment will begin immediately.

9.3 Baseline/Enrollment and Study Evaluations

A study specific Subject Identification Number (SID) will be assigned in consecutive order after informed consent is obtained.

The following data will be collected:

- Patient demographics (at minimum Gender, Age and Race)
- Surgical Date
- Patient Pain Assessment
- Patient self-reported pre-existing conditions (list, if confirmed), if available
- OrthoCor Active System or SOC intervention use details
- Device information (serial number on OrthoCor Active System and OrthoPods)
- Concomitant Pain Medication Use
- Pregnancy Test Results

For those subjects that elect to participate in the research exploratory extension, the patient pain assessment will be collected for another 2 weeks. The extension data will be used for research and publication only.

OrthoCor Active System: Subject(s) are to apply a fully charged brace with a new set of OrthoPods over the affected area for a total of 2 hours at their first convenient opportunity each day. Subject(s) should be instructed to contact the site if they experience unusual sensations or discomfort during the use of the brace.

9.4 Study Exit

Subjects will be considered to have completed and exit the study after 14 consecutive days of OrthoCor Active System or SOC intervention use and the daily OrthoCor Patient Pain eDiary and relevant data is completed.

If significant improvement is noted in the subjects using the OrthoCor Active System after 32 subjects are enrolled into each treatment group, the study will be considered completed and all subjects will have the option to move into the research extension portion. The remaining subjects on SOC will have the ability to move into the active group even if they have not reached or have declined to participate in the research extension.

9.5 Study Schedule of Assessments

In the evening of each day the subject should rate their pain using the provided scale and record their rating in the eDiary. Refer to Table 1 Schedule of Assessments.

Table 1. Schedule of Assessments

Assessments	Screening/Baseline (Day 0)	Day 1 - 14	Research Extension (if applicable) Day 15 – 30
Inclusion/Exclusion Criteria	X		
Demographics	X		
Surgical Date	X		
Pain Assessment	X	X	X
Self-reported Pre-Existing Conditions*	X*		
OrthoCor Active System/SOC Intervention Use		X	X
Device Information	X		
OrthoPod Information	X	X	X
Concomitant Pain Medication Use	X	X	X
Adverse Event, related to the test device		X	X
Pregnancy test for WOCBP	X		

* Information to be collected if available

10.0 ADVERSE EVENTS

Adverse events (AEs) may occur during the study.

Each adverse event will be recorded in the corresponding subject's eDiary. Each adverse event will be assessed by the Investigator as to its relationship and level of relatedness to the investigational device and/or assessment. In addition, the Investigator will identify the date of onset, severity, and duration of the AE. All adverse events will be monitored until they are adequately resolved or explained. If an AE continues after the evaluation, the Sponsor and Investigator should discuss the need and/or methods for continued surveillance of the event.

The Investigator must submit to the Sponsor a report of any Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE) or Unanticipated Adverse Device Effect (UADE) within 24 hours of knowledge of the event.

Sponsor Contact: Udaya Joshi
Telephone: 651-440-9329
Email: ujoshi@CaerusCorp.com

In addition, the Investigator will report adverse events to the reviewing IRB (as applicable) according to the local reporting requirements.

10.1 Adverse Event Definitions

Adverse Event

An adverse event is any undesirable clinical occurrence in a subject whether it is considered to be device-related or not.

Serious Adverse Event

An adverse event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or permanent change
- Congenital Anomaly/Birth Defect
- Required Intervention to Prevent Permanent Impairment or Damage
- Other Serious (Important Medical Events)

Anticipated Adverse Events include those that are reasonably expected to occur in association with the use of OrthoCor Active System (see Appendix B).

Unanticipated Adverse Device Effects (UADE)

Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21CFR812.3).

10.2 Adverse Event Reporting

Adverse events occurring after the baseline assessment but after the study product use will be documented on the appropriate AE report form. All adverse events will be recorded from day 1 until a subject's participation in the trial is considered complete, i.e., at screen failure, completion of study participation (if applicable), subject's demise, or when a subject is discontinued / withdrawn.

It is the responsibility of the Investigators to inform their IRB of adverse events as required by their local IRB procedures.

Anticipated observations related to the study procedure will be tabulated but will not be categorized as adverse events unless they require mitigation by the treating physician or are greater in severity, duration or degree of incidence than anticipated.

Investigators must notify Caerus Corporation (or designee) within 72 hours of discovering any Unanticipated Adverse Device Events (UADE). Investigators are required to submit a report of a UADE to the reviewing IRB as soon as possible, but in no event later than 10

working days after the Investigator first learns of the event. UADEs must be documented as appropriate in the eDiary.

The Sponsor's evaluation of the UADE must be reported to the FDA, all reviewing IRBs, and participating Investigators within 10 working days of knowledge of the event by the Sponsor. All UADE will be reported to the FDA according to regulatory reporting requirements found in CFR 812.46.

10.3 OrthoCor Active System Malfunctions

Any suspected OrthoCor Active System malfunction will be recorded in the eDiary. A list of all adverse events expected in this patient population, adverse events associated with the standard of care and treatment of these patients, as well as with the OrthoCor Active System can be found in Appendix B.

11.0 STATISTICAL ANALYSIS

The primary effectiveness endpoint of this study is the change from baseline of the OrthoCor Active System compared to the SOC intervention results after 14 days.

11.1 Primary Endpoints

The primary objective is to compare the pain assessment scores of the SOC intervention to the OrthoCor Active System pain assessment scores after 14 days.

11.2 Safety Variables

This is a non-significant risk study. Because no additional procedures are required to perform the investigational test, safety will be monitored via the reported Adverse Events in this study. The descriptive table of Adverse Events will be the extent of safety reporting.

11.3 Handling Missing Data

Only subjects with non-missing data for the OrthoCor Active System or the SOC will be used in the statistical analysis, i.e., a complete case analysis.

11.4 Interim Analysis

No interim analyses are planned for this study.

11.5 Demographics

Subject demographics will be summarized using descriptive statistics (mean, median, SD, minimum, maximum), number of subjects for continuous variables (e.g., age), and frequency distributions (number and percentage of subjects) for categorical variables (e.g., gender, race).

11.6 Safety

All adverse events for subjects in the safety population will be reported.

- Serious Adverse Events
- Non-serious Adverse Events Device Related Adverse Event
- Device Related Serious Adverse Events

Results will include the number of subjects experiencing each type of event as well as the number of events.

12.0 RISK – BENEFIT ASSESSMENT

12.1 Potential Risks

There are no known risks associated with the use of the OrthoCor Active System other than the normal minor risks/discomforts associated with the OrthoPods, which could result in localized burns and/or skin sensitivity and irritation.
Potential risks associated with the OrthoCor Active System do not differ from those of the commonly used non-invasive in-vitro devices that provide RF and heat treatment to localized area(s).

The following are adverse events or side effects that may occur as a result of the OrthoCor Active System assessment:

a) Loss of confidentiality due to study participation.

Subjects will be monitored closely as part of this study for the detection of symptoms to allow for early treatment or intervention, if necessary.

12.2 Potential Benefit

There is no direct benefit to the patient for enrolling in this study. However, the study will provide an opportunity to gain a better understanding of the ability of the OrthoCor Active System to effectively be used in the palliative treatment of pain in superficial soft tissue.

12.3 Minimization of Anticipated Risks

Risks associated with the OrthoCor Active System are minimized by design. The Sponsor will monitor the study for any trends that would indicate a safety issue.

13.0 QUALITY ASSURANCE

This study will be conducted in accordance with elements of E6 Good Clinical Practice Integrated Addendum to ICH E6 (R1) (ICH E6(R2), 9 November 2016), abbreviated requirements of 21 CFR 812.2(b) for Non-significant Risk (NSR) device studies, the Declaration of Helsinki, the Belmont Report, and IRB requirements.

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the patient's privacy as far as reasonably practicable. The Sponsor (or designee) and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRF, and original study-relevant medical records/files) as needed. All attempts will be made to preserve patient confidentiality.

All clinical sites are subject to audit by Sponsor (or designee) for protocol adherence, accuracy of data, and compliance with applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for corrective action.

The study protocol, data-recording procedures, data handling as well as study reports are subject to an independent clinical Quality Assurance audit by the Sponsor, its designee, or health authorities.

14.0 ETHICAL CONSIDERATIONS

The rights, safety, and wellbeing of clinical investigation subjects shall be protected consistent with the ethical principles outlined in the Declaration of Helsinki. This shall be understood, observed, and applied at every step in this clinical investigation.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator shall avoid improper influence or inducement of the patient, Monitor, Investigator, or other parties participating in or contributing to the clinical investigation.

The Investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 21 CFR, part 50, the Declaration of Helsinki, CIOMS, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002).

14.1 Institutional Review Board (IRB)

The participating institution must provide for the review and approval of this protocol, the associated informed consent documents, any patient facing materials, and recruitment material, if applicable, by an appropriate Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are placed into use.

14.2 Informed Consent Process

Informed consent will be obtained as outlined in 21 CFR Part 50 and the Good Clinical Practice: Integrated Addendum to ICH E6 (R1) (ICH E6(R2), 9 November 2016).

Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of the OrthoCor Active System will be provided to the subjects. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to collecting study data and/or specimens. Consent forms will be IRB-approved, and the subject or subject's family member/legally authorized representative will be asked to read and review the document.

Upon reviewing the document, the Investigator will explain the research study to the subject and answer any questions that may arise. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate.

Subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.3 Protection of Patient Confidentiality

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each patient shall be preserved in the reports and in any publication. Each patient participating in this study will be assigned a unique identifier. All CRFs will be tracked, evaluated, and stored using only this unique identifier.

The investigational site will maintain a confidential study patient list (paper or electronic) identifying all enrolled patients. This list will contain the assigned study patient's unique identifier and name. The Site Principal Investigator (PI) bears responsibility for keeping this list confidential. This list will not be provided to the Sponsor and is only to be used at the study center.

Monitors and auditors will have access to the study patient list and other personally identifying information of study patients to ensure that data reported in the eDiary corresponds to the person who signed the ICF and the information contained in the original source documents. Such personally identifying information may include, but is not limited to, the patient's name, address, date of birth, gender, race, and medical record number.

Any source documents copied for monitoring purposes by the Sponsor will have patient identifiable information redacted and be identified by using the assigned patient's unique identifier in an effort to protect patient confidentiality.

15.0 STUDY MANAGEMENT

This study will be conducted in accordance with elements of E6 Good Clinical Practice Integrated Addendum to ICH E6 (R1) (ICH E6(R2), 9 November 2016), Abbreviated Requirements of 21 CFR 812 for NSR device studies, the Declaration of Helsinki, the Belmont Report, and any conditions imposed by the reviewing IRB **or** US FDA or other regulatory agency.

Sponsor has the overall responsibility for the conduct of the study according to all applicable regulatory requirements. Sponsor will have certain direct responsibilities and will delegate other responsibilities to the Principal Investigator. Sponsor and Principal Investigator will ensure that the study is conducted according to all applicable regulations. All personnel to participate in the conduct of this clinical trial will be qualified by education and / or experience to perform their tasks.

Sponsor, Investigator, or any person acting for or on behalf of the Sponsor or Investigator shall act in accordance with the applicable standards, guidelines, and regulations.

15.1 Required documents from Investigator (prior to study start)

At a minimum, the following documents will be provided by the investigational site to the Sponsor:

- Signed Investigator Agreement
- Signed Protocol Signature Page
- IRB approval
- IRB approved Informed Consent Form (ICF)
- Investigator's current Curriculum Vitae
- Investigator's current Medical License

15.2 Investigational Device Management

The OrthoCor Active System is FDA cleared for commercial use in the United States. The Sponsor shall maintain adequate records of the disposition of all investigational product for this trial. A copy of the Instructions for Use (IFU) will accompany each study device.

The OrthoCor Active System and pods will be distributed according to the Caerus process for subjects enrolled to use the device. The site will complete the subject enrollment form and email the completed form to OCStudy@medicept.com, the CRO, who will alternatively allocate the OrthoCor Active System or standard of care (SOC) to the enrolled subjects. Then, the Principal Investigator prescribes the enrolled participant who are allocated to the OrthoCor Active System group to receive the device using OrthoCor's Prescriber Prescription Form. This required documentation is then submitted to the Sponsor and the participant will receive a call from the Sponsor to confirm their address. The participant will receive their device in 3 to 5 days.

15.3 Study Training

The study device is intended for use by the patient. The Investigator and study staff will receive Sponsor-led training on the proper use of the device to ensure the study team is familiar with its use prior to study enrollment and participation. The Investigator (or designee) is responsible for the adequate study specific training of each patient. The Sponsor will train each subject on the device usage.

Each study center will undergo protocol initiation including but not limited to a review of the following:

- Study Protocol
- Study Procedures and Assessments
- Process for obtaining Informed Consent and completing Informed Consent Form
- Reporting requirements
- Consent process
- eCRF / eDiary completion and Good Documentation Practices
- Study device overview and usage
- Protection of patient confidentiality

15.4 Data Collection

Study data will be collected using eCRFs and an Electronic Diary (eDiary). The eDiary is designed to accommodate the specific features of the trial design. Modification of the eDiary will only be made if deemed necessary by the Sponsor.

15.5 Monitoring of the Study

Caerus Corporation or designee will monitor the study to ensure that it is conducted in accordance with the protocol and the following guidelines and standards: ISO 14155, the Code of Federal Regulations 21 CFR Part 812 and country specific regulations.

During monitoring visits, the following documents must be made available for review: all CRFs, all source documents such as medical records and clinic charts and any other study related documents. In addition, the OrthoCor Active device and associated supplies accountability will be verified.

Caerus Corporation or designee intends to monitor the investigational site at an interval consistent with the screening rate. If a severe protocol deviation (PD) is noted, Caerus Corporation will recommend corrective action. If there is no response by the Investigator, Caerus Corporation will cease product shipment, discontinue the investigation, and notify the IRB and FDA.

15.6 Investigator Site Termination

Caerus Corporation reserves the right to terminate the investigational site from the study for any of the following reasons:

- Repeated failure to complete eCRF
- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events
- Loss of or unaccountable investigational device inventory
- Repeated protocol violations
- Failure of Investigator to comply with training or Instructions for Use
- Failure to screen at least 10 patients and within any 2-week period
- Persistent non-compliance with the protocol
- Persistent non-compliance with IRB or regulatory requirements

15.7 Site Close-out

At the time of the site close-out visit, the Monitor will collect all outstanding study documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented in a final closeout report.

16.0 STUDY SUSPENSION OR EARLY TERMINATION

The study can be discontinued at the discretion of Sponsor for reasons including, but not limited to, the following:

- Unexpectedly high occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of patients
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to patients (Sponsor may terminate the study immediately)

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all Investigator(s) / Investigational center(s) of the termination or suspension and the reason(s) for this. The IRB shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Site PI / investigational center(s). Regulatory authorities and the personal physicians of the patients may also need to be informed if deemed necessary.

17.0 RESPONSIBILITIES

17.1 Sponsor Responsibilities

Caerus Corporation is the manufacturer of the OrthoCor Active System, the investigational device, and is the Sponsor of this study. Sponsor has the overall responsibility of the study and will work to ensure compliance with the Investigational Plan, elements of Good Clinical Practice: Integrated Addendum to ICH E6 (R1) (ICH E6(R2), 9 November 2016), signed study agreements and 21 CFR 812.2(b).

The Sponsor/CRO will be responsible for, but not limited to, conducting the following tasks:

- Select qualified Investigators
- Select qualified Monitors and other contract study personnel
- Provide the Investigational Plan and any subsequent amendments
- Sign the protocol
- Provide appropriate information and device training to Investigators and site staff
- Promptly inform the Investigators and where applicable Institutional Review Boards (IRBs), if the study is prematurely terminated or suspended and the reason for the termination or suspension
- Provide protocol initiation training to include investigational device instructions for use, the Investigational Plan, eCRF/eDiary completion guidelines, and guidelines for obtaining informed consent
- Coordinate ongoing communication with Monitors and study site to resolve any problems concerning the protocol or data collection. Every effort will be made to ensure compliance with the protocol
- Retain ownership of all clinical data generated in this study and control the use of the data for purposes of regulatory submissions to the FDA.
- Protect patient confidentiality
- Collect, store, and keep secure, at a minimum, the following documents:
  - A current Curriculum Vitae and if applicable, medical license of each Investigator
  - The name of the institutions where the study will be conducted
  - The IRB approval, in writing, and relevant correspondence
  - Correspondence with FDA (as required)
  - Investigator Agreement
  - Protocol Signature Page
  - Appropriate insurance certificates (as necessary) e.g., CLIA/CAP
  - IRB Approved ICF
  - Names / contact information for Monitor(s)
  - Copies of signed and dated eCRFs

- Records of any adverse events and adverse device effects
- Statistical analyses and underlying supporting data
- Final report

17.2 Sponsor Maintenance of Study Records

The Sponsor will be responsible for **maintaining study records** per 21 CFR 812.140(b) and ICH E6 (R1) and ICH E6(R2).

The Sponsor will be responsible for **monitoring the investigation** per 21 CFR 812.46 and ICH E6 (R1) and ICH E6(R2).

The Sponsor will be responsible for **reporting** per 21 CFR 812.50(b).

17.3 Investigator Responsibilities

The Site PI will be responsible for the following tasks:

- Conduct or supervise the trial as written in the clinical protocol.
- Ensure that all associates and study team members are informed about their duties and obligations.
- Understand the investigational device, including potential risks and side effects.
- Ensure that the investigational device is properly handled, dispensed, and administered.
- Monitor and report all adverse events, protocol violations, and unanticipated problems that occur during the study.
- Maintain accurate study records, submit data to Sponsor, if applicable, and make the data available for monitoring and inspection.
- Ensure that the rights, safety, and welfare of human subjects in your study. Obtain informed consent from each subject.
- Complete Data Forms for each subject.
- Maintain the study IRB approval, and inform Sponsor of withdrawal of IRB approval
- Submit progress reports and final reports to IRB and/or Sponsor
- Notify the Sponsor and/or IRB of any study protocol deviations (PDs) or Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE) or Unanticipated Adverse Device Effect (UADE) within 24 hours of knowledge of the event.

17.4 Investigator Maintenance of Study Records

The Investigator will be responsible for **maintaining study records** per 21 CFR 812.140(a) and ICH E6 (R1) and ICH E6(R2).

The Site PI will allow auditing of their clinical investigation procedure(s).

Each Investigator will provide a completed Financial Disclosure statement confirming that they have no personal financial interest connected to the study or Sponsor, prior to study initiation and upon request at later time points in the study if needed.

The Investigator is responsible for maintaining study records for every subject participating in the study. The study center will also maintain ***original*** source documents from which study-related data are derived.

The Investigator must ensure that all study subject records are stored for at least 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. To avoid error, the study site should contact Sponsor prior to the destruction of study records to ensure that they no longer need to be retained. In addition, Sponsor should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

In the event of an FDA audit, the Investigator must allow FDA access to the study records for inspection and copying. The Investigator must inform Caerus Corporation of any FDA audit and provide Caerus Corporation with a copy of Form FDA 483 (List of Observations) if issued.

18.0 DATA MANAGEMENT

Data will be handled as applicable, per ICH E6 (R1) and ICH E6(R2).

18.1 Data Entry

Qualified personnel assigned by the Principal Investigator and/or the Sponsor will perform data entry.

All data will be collected on source documents and source document verification (SDV) will be conducted to ensure data collected are reliable and allow reconstruction and evaluation of the study. An eDiary will be completed for every subject who signs a written Informed Consent Form and is enrolled in the study. Data for this study will be entered and accepted from the site into a 21 CFR Part 11 Compliant Electronic Diary (eDiary) system. The study coordinator shall complete the eCRF by adding or updating subject information during screening.

18.2 Data Cleaning and Monitoring

Once data has been entered, the Monitor shall view the eCRF and verify the data with the source documents. In the SDV process, information reported by the Investigator is compared with the original records to ensure that it is complete, accurate, and valid. Throughout the course of the study Data Management shall also review the data. This review will ensure that missing out-of-range or incomplete data is queried and resolved.

A database lock will occur once all data has been entered, SDV is completed, all queries resolved, quality assurance procedures completed and the data has been deemed clean.

All study related data should be entered in the EDC within 5 business days of the subject's study enrollment.

The Monitor shall generate queries for data errors and discrepancies discovered in their review of source documents. When queries are necessary, the Monitor will select the appropriate field and generate an electronic query. Upon notification, the Site Coordinator will respond with a reason for the discrepancy and document that data is correct as documented or will provide a corrected resolution to the data field. The Monitor shall review the resolution and close the query, if appropriate. If additional information is required, the Monitor will continue the process until all data requirements are satisfied.

Queries will also be generated by data management, for mistakes and discrepancies encountered during data review and through logic checks. When queries are necessary, the data manager will select the appropriate field and generate the electronic query. Upon notification, the site coordinator will respond with a reason for discrepancy and document that data is correct as documented or will provide a corrected resolution to the data field. The data manager shall review the query resolution and close the query when appropriate. If further information is required for resolution to the query the data manager will initiate the process until all data requirements are satisfactory.

18.3 Final Clinical Study Report

A final report will be completed, even if the study is prematurely terminated.

18.4 Publication Policy

Information concerning the study device, patent applications, processes, unpublished scientific data, the Protocol, and other pertinent information is confidential and remains the property of the Sponsor.

At the conclusion of the trial, the results may be prepared and used in support of an FDA submission and provided at a major meeting(s). The publication of results from any center experience within the trial is not allowed unless there is written consent from the Sponsor.

A publication strategy plan will be developed as a collaboration between the Principal Investigators and the Sponsor, Caerus Corporation.

19.0 REFERENCES

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2. Fred R. Nelson, Raimond Zvirbulis, Arthur A. Pilla (Rheumatol Int 2013). Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: a randomized double-blind pilot study, 33(8), 2169–2173. doi:10.1007/s00296-012-2366-8
3. Berish Strauch; Charles Herman; Richard Dabb; Louis J. Ignarro; Arthur A. Pilla (Aesthet Surg 2009). Evidence-Based Use of Pulsed Electromagnetic Field Therapy in Clinical Plastic Surgery, 29(2), 135–143. doi:10.1016/j.asj.2009.02.001
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5. State of The Art in Electromagnetic Therapeutics: Soft Tissue Applications. Arthur A Pilla. Bioelectrochemistry Laboratory, Department of Orthopedics, Mount Sinai School of Medicine, New York, NY 10029 USA. In: Electricity and Magnetism in Biology and Medicine, F Bersani, ed. Plenum, NY, 1999, pp. 871-874.
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20.0 APPENDICES

APPENDIX A. OrthoCor Active System - INSTRUCTIONS FOR USE (IFU)

APPENDIX B. ADVERSE EVENTS

APPENDIX A.
OrthoCor Active System - INSTRUCTIONS FOR USE (IFU)

APPENDIX B.

Adverse Events

The following adverse events are unexpected but may occur with use of OrthoCor Active System:

- Patient injury during use such as skin irritation or burns.