Official Title of the study:	OsteoCool Tumor Ablation Post-Market Study (OPuS One)
NCT Number:	NCT03249584
Date of Document:	20 January 2019
Document Type:	Study Protocol

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	**O**steoCool Tumor Ablation **P**ost-Market **S**tudy (OPuS One)
Clinical Investigation Plan Identifier	MDT16075
Study Product Name	Medtronic OsteoCool™ RF Ablation System
Sponsor/Local Sponsor	United States (Sponsor) Medtronic, Inc. 7000 Central Ave NE Minneapolis, MN, 55432 USA 763-514-4000 Europe (Local Sponsor): Medtronic International Trading Sàrl Route du Molliau 31 Case Postale CH-1131 Tolochenaz, Switzerland (41 21)802 7000 Canada (Local Sponsor) Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada 905-460-3800
Document Version	**4.0**
Document Version Date	***20 January 2019***
Document Reference Number	*NA*
Global Principal Investigator	[redacted]

Confidentiality Statement

Table of Contents

List of Figures:

List of Tables:

1. Investigator Statement

Study product Name	OsteoCool™ RF Ablation System
Sponsor	Medtronic, Inc.
Clinical Investigation Plan Identifier	MDT16075
Version Number/Date	Version 4.0/20 January 2019

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the applicable regulatory guidelines under which the study is being conducted, the ethical principles that have their origin in the Declaration of Helsinki.

In the US, the study will be conducted in accordance with 21 CFR§11 Electronic Records, Electronic Signatures, 21CFR§50 Protection of Human Subjects, 21 CFR§54 Financial Disclosure by Clinical Investigators, 21CFR§56 IRB, and 21CFR§803 Medical Device Reporting.

In Europe, the study will be conducted in accordance with 21 CFR§11 Electronic Records and Electronic Signatures, 21 CFR§54 Financial Disclosure by Clinical Investigators, and any regional or national regulations, as appropriate.

In Canada, the study will be conducted in accordance with Canada Medical Devices Regulations, 1998 (SOR/98-282), and the Guidance document for Mandatory Problem Reporting for Medical Devices, 2011(H164-145/201E).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

2. Glossary

Term	*Definition*
ADE	Adverse Device Effect
AE	Adverse Event
BPI	Brief Pain Inventory (Short form)
CAN	Canada
CE	Conformité Européenne
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan ('Protocol')
CR	Complete Response
CT	Computer Tomography
DD	Device Deficiency
EBRT	External Beam Radiation Therapy
EC	Ethics Committee
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol five dimensions with five levels questionnaire
EORTC-QLQ-C15-PAL	European Organization for Research and Treatment of Cancer Care Quality of Life Questionnaire for palliative care
EUR	Europe
FDA	Food and Drug Administration
HCO	Health Care Organization
HCP	Health Care Professional
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
IFU	Instructions for Use

Term	*Definition*
IR	Indeterminate Response
IRB	Institutional Review Board
KPS	Karnofsky Performance Scale
MedDRA	Medical Dictionary for Regulatory Affairs
MCID	Minimal Clinically Important Difference
MRI	Magnetic Resonance Imaging
NPRS	Numeric Pain Rating Scale
OMED	Oral Morphine Equivalent Dose
PET	Positive Emission Tomography
PKP	Percutaneous Kyphoplasty
POST	Power-On-Self-Test
PP	Pain Progression
PR	Partial Response
PT	Preferred Term
PTH	Parathyroid Hormone
QOL	Quality of Life
RC	Research Coordinator
RDC	Oracle Clinical Remote Data Capture
RF	Radiofrequency
RFA	Radiofrequency Ablation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SP	Statistical Analysis Plan
SIR	Society of Interventional Radiology
SOC	System Organ Class

Term	*Definition*
SRE	Skeletal Related Events
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analog Scale
VBM	Vertebral Body Metastases

3. Synopsis

Title	**O**steoCool Tumor Ablation **P**ost-Market **S**tudy (OPuS One) MDT16075
Clinical Study Type	Post-market
Product Name	Medtronic OsteoCool™ RF Ablation System
Sponsor	Medtronic, Inc.
Local Sponsor	United States (Sponsor) Medtronic, Inc. 7000 Central Ave NE Minneapolis, MN, 55432 USA Europe (Local Sponsor): Medtronic International Trading Sàrl Route du Molliau 31 CH-1131 Tolochenaz, Switzerland Canada (Local Sponsor) Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada
Indication under investigation	US Indication: The OsteoCool™ RF Ablation System is intended for: • *Palliative treatment in spinal procedures by ablation of metastatic malignant lesions in a vertebral body*

	• *Coagulation and ablation of tissue in bone during surgical procedures including palliation of pain associated with metastatic lesions involving bone in patients who have failed or are not candidates for standard therapy* • *Ablation of benign bone tumors such as osteoid osteoma.* <u>Europe and Canada indication:</u> • *The OsteoCool™ RF Ablation System is intended for ablation of benign bone tumors such as osteoid osteoma and palliative treatment by ablation of metastatic malignant lesions involving bone, including the vertebral body.*
Investigation Purpose	To evaluate the effectiveness of the Medtronic OsteoCool™ RF Ablation System.
Product Status	All devices used in this study are commercially available and will be used within the intended approved indication as listed in the Instructions for Use (IFU).
Primary Objective	To demonstrate an improvement from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in only the thoracic and/or lumbar vertebral body(ies). Worst pain score at the target treatment site will be collected from the Brief Pain Inventory (BPI).
Secondary Objective	To characterize change from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in the periacetabulum, iliac crest, and/or sacrum, and for benign bone tumors. Worst pain score at the target treatment site will be collected from the BPI.
Additional Measures	

	• [redacted]
Safety Measure	To characterize incidence of all device, procedure and/or therapy related adverse events and device deficiencies from enrollment to the 12-Month Visit.
Study Design	Prospective, multi-center, post-market, single-arm study. Each subject's participation in the study is expected to last approximately 1 year from the date of the OsteoCool procedure. Follow-up assessments will occur upon discharge post procedure (worst pain only), 3 days, 1 week and 1-, 3-, 6-, and 12-months post procedure. The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 5 years. The completion of the study is defined as the approval of the Final Study Report and closure of all sites.
Sample Size	Up to 250 subjects in approximately 20 sites.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** In order to be included in this study, a patient must meet the following inclusion criteria: 1. Candidate for OsteoCool RF ablation per the labeled indication applicable in their respective country/region 2. A. Metastatic lesions targeted for treatment must be located in the thoracic and/or lumbar vertebral body(ies), periacetabulum, iliac crest, and/or sacrum OR benign bone tumors– no restrictions on location of lesion 3. Report worst pain score ≥4/10 at the target treatment site within the past 24 hours

	4. Localized pain resulting from not more than two sites of metastatic disease 5. Have Karnofsky score ≥40 at enrollment (not applicable for subjects with benign bone tumors) 6. Willing and able to provide a signed and dated informed consent, comply with the study plan, follow up visits and phone calls 7. At least 18 years old at the time of informed consent **Exclusion:** In order to be included in this study, a patient must not present with any of the following exclusion criteria: 1. A. Implanted with heart pacemaker or other implanted electronic device (Europe and Canada only) 2. Use of OsteoCool in vertebral body levels C1-C7 3. Multiple myeloma, solitary plasmacytoma, or primary malignant lesions in the index vertebra or bone. 4. Active or incompletely treated local infection at the planned treatment site(s) and/or systemic infection 5. Planned treatment site(s) accompanied by objective evidence of secondary radiculopathy or neurologic compromise 6. Planned treatment site(s) associated with spinal cord compression or canal compromise requiring decompression 7. Fractures due to prostatic cancer or other osteoblastic metastases to the spine. Metastatic lesions originating in the prostate that are osteolytic or of mixed origin are eligible for the study 8. Pregnant, breastfeeding, or plan to become pregnant during the study duration 9. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results* 10. Any condition that would interfere with the subject's ability to comply with study instructions or might confound the study interpretation *Subjects in concurrent studies can only be enrolled with permission from Medtronic. Please contact Medtronic's study manager to determine if the subject can be enrolled in both studies.
Study Procedures and Assessments	Upon obtaining informed consent, each subject will complete an Enrollment/Baseline visit, OsteoCool procedure visit (Day 0), and 5 post-procedure visits (3 days, 1 week, 1-, 3-, and 6- month clinic visits), and a final post-procedure study visit (12 months) for a total of 8 study related visits.

Safety Assessments	Collect all device, procedure and/or therapy related adverse events and device deficiencies from enrollment to the 12-Month Visit.
Statistics	Hypothesis testing will be performed on the primary objective, requiring approximately 52 treated subjects to achieve 35 completing the 3-Month visit. Descriptive statistics for the secondary objective and additional measures will be reported. Device, procedure and/or therapy related adverse events and device deficiencies will be presented in summary tables.

4. Introduction

4.1. Background

Most patients who die from cancer do so not because of the tumor in the primary site, but rather because it has spread to other sites.[1] Patients with advanced breast and prostate cancers almost always develop bone metastases, and the major tumor burden at the time of death will be in bone.[1] Other tumors that commonly metastasize to the spine are from the lung, and kidney.[2] The prevalence of bone metastasis has increased over time primarily because cancer survival rates have increased.[1] Patients with bone metastases suffer from serious related events such as pain, fractures, spinal cord compression, and hypercalcemia.[3]

Goals for the treatment of bone metastases are pain relief, preservation of mobility and function, prevention of future complications, optimized quality of life (QOL), maintenance of skeletal integrity, and minimization of hospitalization.[4] Surgical treatments such as vertebrectomy, reconstructions with cages, tumor prostheses, pedicle screws or other types of extensive therapies are available to assist with pain relief and strengthen skeletal integrity; however these are associated with long recovery periods and high morbidity and mortality.[5,6]

External beam radiation therapy (EBRT) is the standard of care in the treatment of bone metastases, but it has several important limitations.[7] Pain relief with EBRT can take up to 4-6 weeks after treatment completion.[8] Side-effects of radiation include risk of bone fractures and a potential inability to repeat radiation therapy at the same site if the pain persists because of tissue tolerance.[9]

There are several minimally invasive ablation procedures that can be used to treat painful bone metastasis including thermal-, laser, cryo-, and radio frequency ablation. Recent treatment guidelines have outlined where in the treatment paradigm ablation can be considered.[10]

Radiofrequency (RF) is a high-frequency alternating current that is passed from the needle electrode into the surrounding tissue resulting in frictional heating and necrosis. Several small observational studies have reported pain relief,[9,11,12,13,14,5] mood and pain intensity improvements[11] and decreased

opioid use.[9, 14] The clinical goal of RF ablation in vertebral metastases is primarily pain reduction and tumor shrinkage before stabilization.[15,16]

The OsteoCool™ RF Ablation system is indicated in the United States (US), Europe (EUR) and Canada (CAN) for patients with metastatic malignant lesions in a vertebral body, painful metastatic lesions involving bone (in the US, patients with metastatic lesions involving the bone must have failed or were not candidates for standard therapy) and benign bone tumors such as osteoid osteomas. The system offers cooled radiofrequency (RF) ablation technology with simultaneous, dual-probe capabilities providing procedural flexibility and predictable, customized treatment. The OsteoCool RF Ablation Probe uses a coaxial, bipolar technology that delivers localized tumor ablation and automatically moderates power to keep RF heating within the desired treatment range, reducing risks of potential thermal damage to adjacent tissue. A differentiating feature of the OsteoCool system is the active tip of the RF Ablation Probe that is internally-cooled with circulating water. RF energy heats the tissue while circulating water moderates the temperature in close proximity to the active tip. This combination creates large volume lesions without excessive heating at the active tip.

To date no study has evaluated long-term patient outcomes after RF ablation with the OsteoCool™ RF Ablation system.

4.2. Purpose

The purpose of this prospective, multi-center, non-randomized, single arm study is to evaluate the effectiveness of the Medtronic OsteoCool™ RF Ablation system.

The expected study commitment for each subject is approximately 1 year post RF ablation. In addition, predictive and sub-group analyses will be conducted to determine characteristics related to outcomes.

Data from this study may be used to address regulatory (e.g., Draft European Medical Device Regulations), reimbursement and/or clinical data needs as identified through different regions.

This study will be posted on ClinicalTrials.gov as part of Medtronic's commitment to full disclosure for ongoing studies that meet the requirements for public posting.

4.3. Preclinical Data

Radiofrequency ablation functions by directing alternating electrical current to locally excite ionic cellular components, relying on successful heat conduction and completion of an electric circuit.[17] Two preclinical studies were conducted to evaluate the efficacy and safety of this system.

Pezeshki et al[18] (2014) evaluated the feasibility, efficacy and safety of a novel bipolar-cooled radiofrequency device with the use of a porcine vertebral model and the ability of magnetic resonance imaging (MRI) to represent histological outcomes of RF ablation treatment. Three noncontiguous lumbar vertebrae in six Yorkshire pigs were treated with RF ablation via a transpedicular approach. MRIs and neurological assessments were conducted pre- and post-treatments and evaluated immediately post-procedure and 14 days after the procedure. Imaging and histologic evidence demonstrated a well-confined zone of ablation within the vertebral body that measured up to 2.5 cm in length. The average volume calculated based on segmentation of the MRI for all treated levels was 2.24±0.90 cm^3. RF

ablation was successfully applied within the vertebrae of all six pigs. Neurologic examination demonstrated normal behavior in all pigs' pre-treatment, post-treatment, and 14 days post-procedure indicating that the treatment did not damage any neural tissues.

Pezeshki et al[17] (2015) aimed to determine the effects of bipolar cooled radiofrequency ablation on bone and tumor cells in a diseased lapine model, and to compare MRI effect in reflecting histological ablation within the diseased skeleton. Twelve New Zealand white rabbits received a single injection of tumor cells (VX2) into one randomly selected femur and observed for 14 days. Rabbits were randomized to one of four experimental groups: tumor-bearing RF ablation treated; healthy RF ablation treated; tumor-bearing shams; and healthy sham group. Treatment effects were evaluated by MRI on day 28. Animals were euthanized and bone tissues harvested. Large volumes of thermal ablation were achieved on evaluation. An eight-fold reduction in tumor growth resulted in RF ablation treated animals compared to tumor-bearing sham controls.

4.4. Clinical Studies

Bagla et al (2016)[19] enrolled fifty patients at eight sites in the US between August 2013 and September 2014. Inclusion criteria were painful vertebral body metastases (VBM) in at least one thoracolumbar vertebra with the pain concordant to the metastatic lesion. Imaging was performed prior to the procedure to confirm that the focal pain correlated with the cross-sectional imaging and treatment plan. Ablation within each vertebral body was performed using the STAR Tumor Ablation System (DFINE, San Jose, CA). In most cases (47/50), cement augmentation (StabiliT® Vertebral Augmentation system, DFINE, San Jose, CA) was performed following ablation. Patients completed four validated clinical instruments to measure their pain: Numeric Pain Rating Scale (NPRS), disability (Modified Oswestry Disability Index) and quality of life (FACT-G7 and FACT-BP (FACIT, Elmhurst, IL)). Follow-up assessments occurred at discharge (NRPS only), 3 days, 1 week, 1 and 3 months post RF ablation. Complications were recorded through the 3-month follow-up period and graded using the classification system used by the Society of Interventional Radiology (SIR) and the National Cancer Institute's common Toxicity criteria.

Over 50 % of the primary cancer types originated from breast, kidney and lung. Sixteen patients (32 %) received prior radiation therapy at differing times prior to Radiofrequency Ablation (RFA) treatment. Thirty-four patients had a single VBM, 13 patients had two VBM, and three patients had three VBMs for a total of 69 vertebrae treated, 57 % of which were in the lumbar region of the spine. Of the thoracic VBMs, all were in the T6–T12 range except for one (T1). All patients were treated in a single session under either conscious sedation (n = 35, 70 %) or general anesthesia (n = 15, 30 %).

Patients experienced a mean pain score of 5.9 on a 0–10 scale at baseline. Pain decreased to a mean of 3.7 immediately after the procedure with additional reduction to 2.1 at month 3. On a patient-by patient basis, pain relief was rapid with 32/49 (65%) of the patients experiencing ≥2 point change within 3 hours of treatment. Pain Scores decrease was statistically significant at each follow-up time point. Of the patients who received RFA without cement augmentation, all patients (3/3) demonstrated clinical success immediately after the procedure with a mean improvement of 4.3 NPRS points. At the last follow-up visit for all non-cemented patients, mean improvement was 5.0 NPRS points.

The modified ODI improved from 52.9 at baseline to 37.0 ($p<0.08$) at the 3 month visit. The FACT-G7 improved from 10.9 to 16.2 ($p = 0.0001$) and the FACT-BP improved from 22.6 to 38.9 ($p<0.001$).

There were six adverse events reported in six patients during the course of this study. This included: pain outside the target vertebrae due to progression of the primary or other metastatic disease ($n = 3$), ruptured disk ($n = 1$) adjacent to the index vertebra, neuropathic pain ($n = 1$) and syncope ($n = 1$). The ruptured disk was present prior to treatment of the index vertebrae, became painful (between the month 1 and month 3 visit) and was resolved following bilateral nerve blocks. Neuropathic pain was present prior to the procedure and intermittent after the procedure ($n = 1$). The operating physicians deemed five of the adverse events as unrelated and one, the ruptured disk, as unlikely related to the RFA and/or vertebral augmentation procedures.

The authors concluded that radiofrequency ablation with or without vertebral augmentation was a safe, effective and durable treatment for patients with painful metastatic vertebral body tumors.

David et al (2016)[20] compared 26 patients who received RF ablation followed by either vertebroplasty (35 levels) or osteoplasty (4 levels) vs. 56 patients who had vertebroplasty alone (142 levels). There were fewer posterior and venous cement leaks in the RF ablation group. There were no differences in the rate of cement leakage between the two groups. Average pain scores in the RF ablation group dropped from 8.4 to 4.0 from pre- to post-RF ablation procedure ($p<0.0001$). Pain scores were not obtained in the conventional vertebroplasty group as they were only retrospectively reviewed through the database. The study concluded that RF ablation using a bipolar device is safe and allows for controlled injection of cement into a preformed thermal cavity with a significant decrease in venous and posterior cement leaks.

Dierselhuis et al (2014)[21] enrolled 20 patients in a pilot study evaluating the efficacy of RF ablation in the treatment of atypical cartilaginous tumors of the long bones. After inclusion, biopsy and radiofrequency ablation were performed, followed three months later by curettage and adjuvant phenolisation. The primary endpoint was the proportional necrosis in the retrieved material. Secondary endpoints were correlation with the findings on gadolinium enhanced MRI, functional outcome and complications.

Results at 3-months post procedure showed 95% to 100% necrosis was obtained in 14 of the 20 patients. MRI demonstrated 91% sensitivity and 67% specificity for detecting residual tumor after curettage. The mean functional outcome score (as measured by the Musculoskeletal Tumor Society Scoring System) six weeks after radiofrequency ablation was 27.1 (ranged from: 23-30) compared with 18.1 (range: 12-25) after curettage ($p< 0.001$). No complications occurred after ablation, while two patients developed a pathological fracture after curettage. Dierselhuis et al summarized that RF ablation could provide better local tumor control, while improving functional outcomes.

A retrospective study of 26 patients with thoracolumbar vertebral metastatic tumors treated with RF ablation and percutaneous kyphoplasty (PKP) was conducted by **Zheng et al. (2014)**[22] between February 2005 and January 2009. Patients underwent image-guided RF ablation with PKP under general anesthesia. Patients were followed for a minimum of 3 months and up to 18 months. The exact model of the RF ablation was not specified.

RF ablation with PKP was successful in all patients n=26, and no secondary surgery was reported at any time point during follow-up. A mean of 2.69±0.93 ablations was performed per patient. The ablation procedure required a mean of 15.08±4.64 min, while the injection of bone cement required a mean of 6.73±0.83 min, for a mean total operating time of 47.77±7.13 min. Postoperative Visual Analog Scale (VAS) scores were significantly lower on day 3, week 1, and months 1, 3, and 6 (P<0.01), without any complications or tumor recurrence. The study concluded that RF ablation with PKP was safe and effective.

Deschamps et al (2014)[23] reviewed the medical records of all patients who had undergone thermal ablation of bone metastasis at their institution between September 2001 and February 2012. Subjects who were treated palliatively were excluded; only subjects who were treated with a curative intent were included. The goal was to achieve complete treatment of all bone metastases (group 1) or only of bone metastases that could potentially lead to Skeletal Related Events (SRE) (group 2). The patients in group 1 had oligometastatic disease (defined as 1–5 lesions besides the primary tumor) and the strategy was to obtain no evidence of clinical disease using loco-regional therapies (namely thermal ablation for bone metastases). Patients in group 2 had bone and extraskeletal metastases that could not all be cured using loco-regional therapies. For patients in group 2, the bone metastases were treated at the discretion of the multidisciplinary meeting according to the local risk of SRE. Patients had undergone either radiofrequency ablation or cryoablation. A baseline Computer Tomography (CT) was performed at the beginning of all thermal ablation procedures.

Radiofrequency ablation was performed using a straight and perfused needle electrode (Cool –Tip RF system®, Covidien, Boulder, Co). Cryoablation was performed under conscious sedation using one or several cryoablation needles (icesphere® or icerod®, Galil Medical, Yokneam, Israel). Cementoplasties were performed in association with the thermal ablations.

Between September 2001 and February 2012, 89 consecutive patients had undergone 96 sessions of curatively intended thermal ablation of 122 bone metastases. The median follow-up was 22.8 months [IQR=12.2-44.4]. Seventy-four metastases were treated using radiofrequency ablation and 48 with cryotherapy. The cementoplasties were performed in association with the thermal ablation in 38 metastases. Follow-up imaging had been performed every 4 months on average. The treatment failures were diagnosed based on an increase of bone metastasis diameter compared to the baseline CT in 14% of the cases and on residual tumor uptake in 86%. In the intent-to-treat analysis, the 1-year complete treatment rate was 67% (95%; CI: 50-76%). In the multivariate analysis, the factors associated with a lower risk of treatment failure were metachronous bone metastasis (p=0.004), no cortical bone erosion (p=0.01), the maximum diameter at baseline CT <20 mm (p= 0.001), no critical neurological structures in the vicinity (p=0.002) and the metastases in group 1 patients (p=0.02). A higher risk of treatment failure was not related to patient characteristics, the site of the primary tumor, previous treatment with external radiotherapy, the location of the bone metastasis, the previous number of bone metastases in the previous medical history, the condensation appearance at CT or to the thermal ablation technique used (radiofrequency ablation or cryotherapy). Deschamps et al. concluded that thermal ablation should be included in the therapeutic arsenal for the care of bone metastases.

Anchala et al (2014)[24] conducted a retrospective chart review at 5 institutions identifying subjects who received RF ablation as a treatment of osseous metastatic disease using the STAR Tumor Ablation

System (DFINE, San Jose, CA) between March 2012 and March 2013. One hundred and twenty-eight osseous spine metastatic lesions were treated in 92 patients with or without concurrent vertebral augmentation. Subjects were followed at 1 week, 1 month and 6 months post-procedure. RF ablation was technically successful in all lesions without complication or thermal injury. Statistically significant decreases in VAS scores at all follow-up visits were reported. Post-ablation imaging confirmed size of ablation zones consistent with that measured by the thermocouples. Anchala et al demonstrated that metastatic osseous lesion can safely be effectively treated with RF ablation.

Gazis et al (2014)[25] prospectively evaluated 36 patients with secondary tumor involvement of the spine treated with RF ablation between November 2006 and April 2009 at one institution. The aim of the study was to show that bipolar RF ablation safely treats spinal lesions and creates a predictable ablation zone. All ablations were performed using the CelonLab Power and Celon Aquaflow III systems (Celon AG Medical Instruments, Teltow, Germany). MRI was performed pre and post-procedure. A review of the MRI indicated that the extent of the ablation zone did not cross the peri-interventional planned dorsal and ventral boundaries in all cases. Pain reduction was observed in 19 cases (52.8%); no change was reported in 13 cases (36.1%); and pain worsening was reported in 4 cases (11.1%). No complications regarding locomotory restriction or decline of sensitivity was reported. The investigators concluded that ablation of tumorous masses adjacent to vulnerable structures was feasible and predictable using bipolar RF ablation but additional studies on the treatment of high-risk tumors using this technique are necessary.

Hillen et al (2014)[26] retrospectively evaluated the use and safety of a targeted RF ablation device for metastatic posterior vertebral body tumors. Fluoroscopic or computed tomography–guided targeted RF ablation was performed in 26 patients (47 tumors) using the STAR Tumor Ablation System (DFINE, San Jose, California) over a period of 12 months from June 2012 through June 2013. Pain scores and adverse events were obtained immediately postop and by telephone 1 week and 1 month after the procedure. Four patients developed transient radicular symptoms after ablation which resolved with transforaminal blocks. No permanent neurologic injuries were reported. Intra-procedural imaging demonstrated that the articulating bipolar instrument could be navigated into the posterior vertebral body tumors with a transpedicular approach. Post-ablation imaging confirmed necrosis within the ablation zone. Three patients showed progression of disease at the treated levels during follow-up. Targeted RF ablation with a newly developed articulating device was determined to be both feasible and safe for the treatment of painful posterior vertebral body metastatic tumors.

Wallace et al (2016)[27] reviewed the tumor ablation databases of two institutions identifying patients who underwent combination acetabular radiofrequency ablation and cementoplasty using the STAR Tumor Ablation and StabiliT Vertebral Augmentation Systems (DFINE; San Jose, CA) between April 2012 and April 2015. Pre- and post-procedure pain scores were measured using the Numeric Rating Scale (11-point scale) and compared. Partial pain improvement was categorically defined as ≥2-point pain score reduction.

A total of 12 patients were treated with combination RF ablation and cementoplasty. The median tumor volume was 54.3 mL (range: 28.3–109.8 mL). Pre- and post-procedure pain scores were obtained from 92% (11/12) of the cohort. The median pre-procedure pain score was 8 (range: 3–10). Post-procedure pain scores were obtained 7 days (82%; 9/11), 11 days (9.1%; 1/11) or 21 days (9.1%; 1/11) after

treatment. The median post-treatment pain score was 3 (range: 1–8), a statistically significant difference compared with pre-treatment (P=0.002). Categorically, 73% (8/11) of patients reported partial pain relief after treatment. No immediate symptomatic complications occurred. Three patients (25%; 3/12) were discharged to hospice within 1 week of treatment. No delayed complications occurred in the remaining 75% (9/12) of patients during median clinical follow-up of 62 days (range: 14–178 days).

Wallace et al (2016)[28] retrospectively conducted a chart review at one institution identifying subjects treated with RF ablation for a diagnosis of osteoid osteoma. Between April 2012 and May 2015, 18 osteoid osteomas were radiofrequency ablated with the STAR Tumor Ablation System (DFINE, San Jose, CA). The mean patient age was 24.1 ±14.9 years (range: 5.5-58.2 years). Lesion locations included the femur (50%; 9/18), tibia (22%; 4/18), cervical spine (11%; 2/18), calcaneus (5.5%; 1/18), iliac bone (5.5%; 1/18), and fibula (5.5%; 1/18). Eighty-nine percent of tumors (16/18) were extra-articular, and two tumors (11%; 2/18) were located within the hip joint.

All ablation procedures were technically successful. Sixty-one percent of tumors (11/18) were cumulatively ablated for less than 6 min. During ablation, the median maximum temperatures measured at the thermocouples located 10 and 15 mm from the center of the ablation volume were 68 C (range: 51–94 C) and 47 C (range: 42–55 C), respectively. Clinical follow-up of more than 30 days was obtained for 89% (16/18) of patients. For these patients, median clinical follow-up was 56 days (range: 34–91 days). All of these patients reported complete resolution of symptoms.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

To demonstrate an improvement from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in only the thoracic and/or lumbar vertebral body(ies).

Worst pain score at the target treatment site will be collected from the Brief Pain Inventory (BPI).

5.1.2. Secondary Objective(s)

To characterize change from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in the periacetabulum, iliac crest, and/or sacrum, and for benign bone tumors.

Worst pain score at the target treatment site will be collected from the BPI.

5.1.3. Additional Measures

- [redacted]

[redacted]

5.1.4. Safety Measure

To characterize incidence of all device, procedure and/or therapy related adverse events and device deficiencies from enrollment to the 12-Month Visit.

5.2. Endpoints

5.2.1. Primary Endpoint

The primary endpoint of the study is the improvement of worst pain score at the target treatment site 3 months post RF ablation for subjects with metastatic lesions in only the thoracic and/or lumbar vertebral body(ies).

5.2.2. Secondary Endpoints

The secondary endpoint of the study is to characterize change in worst pain score at the target treatment site 3 months post RF ablation for subjects with metastatic lesions in the periacetabulum, iliac crest, and/or sacrum, and/or for benign bone tumors.

5.2.3. Additional Measures

[redacted]

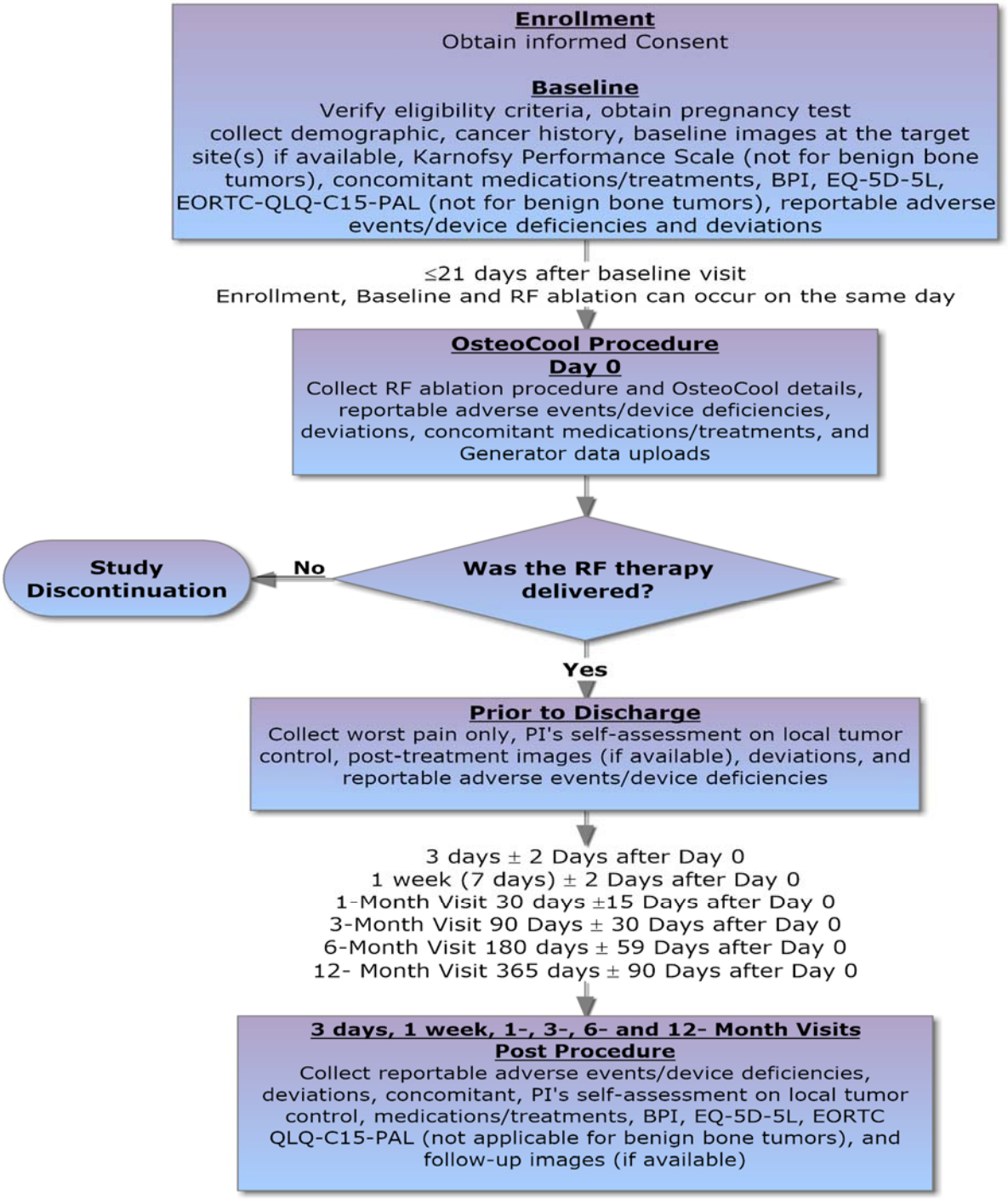
6. Study Design

This is a prospective, multi-center, non-randomized, post-market, single arm study designed to provide effectiveness outcomes on the Medtronic OsteoCool™ RF Ablation system.

The study will evaluate up to 250 subjects at approximately 20 study sites in the United States (US), Europe (EUR), and Canada (CAN). Patients that meet all inclusion criteria, do not meet any exclusion criteria, and provide written informed consent (IC) will be enrolled in the study. Commercially available study devices will be used within the intended approved indication as listed in the IFUs applicable in each country/region.

Figure 6-1 outlines the study design and required follow-up requirements.

Figure 6-1: Study Design



6.1. Duration

The start of the study for each subject is defined as the date the subject first signs the informed consent. Enrolled subjects who do not meet baseline eligibility or who do not undergo the OsteoCool procedure will be exited from the study (e.g. RF therapy was not delivered). The completion of the study for each subject is defined as the conclusion of the 12 Month Visit (Study Exit). Each subject's participation in the study is expected to last approximately 1 year from the date of the OsteoCool procedure. Each subject will be evaluated prior to the OsteoCool procedure, during the procedure, prior to hospital discharge, 3 days, 1 week, 1-, 3-, 6-, and 12-months post procedure.

The estimated time needed to enroll all subjects is approximately 3 years. The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 5 years. The completion of the study is defined as the approval of the Final Study Report and closure of all sites.

6.2. Rationale

The OsteoCool™ RF Ablation system has 510k regulatory clearance in the United States, Conformité Européenne (CE) mark in Europe, and Health Canada License in Canada. The goal of this study is to collect real-world outcomes among a cohort of patients in the US, EUR and CAN with metastatic malignant lesions in a vertebral body, painful metastatic lesions involving bone (in the US, patients with metastatic lesions involving the bone must have failed or were not candidates for standard therapy), and benign bone tumors such as osteoid osteoma who receive treatment with the OsteoCool™ RF Ablation system. Additionally, the study will collect device, procedure and/or therapy related adverse events and device deficiencies. Lastly, subject outcomes (such as pain relief, quality of life, and function) will be evaluated using validated assessment measures. Published data evaluating the real-world use of RF ablation in this patient population is limited. As such, a prospective, single-armed study designed to capture real-world outcomes is justified.

7. Product Description

7.1. General

The figure and tables below describe the components of the OsteoCool™ RF Ablation system.

Any future approved models may be used in the study if commercially available and if the modifications do not have the potential to affect the study results.

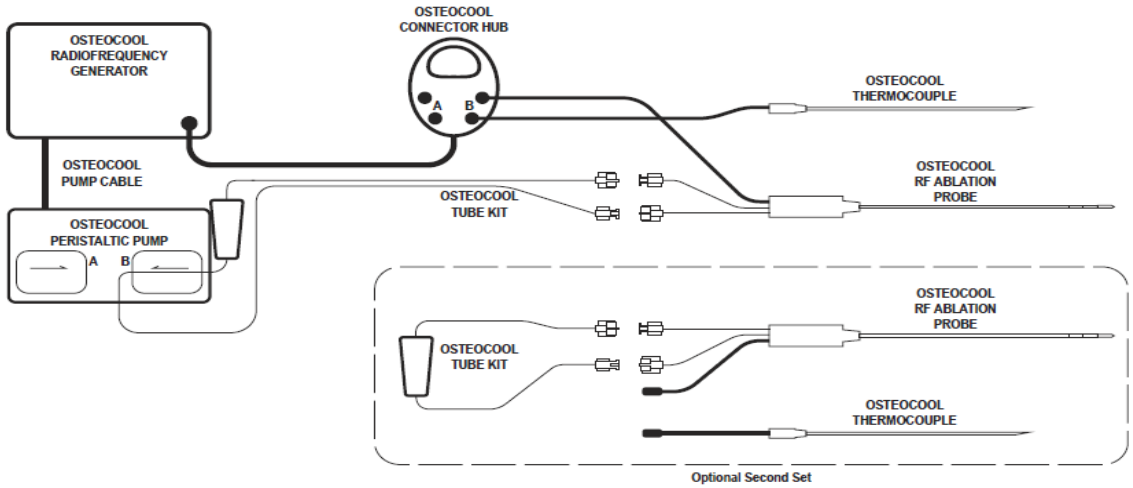


Figure 7-1: OsteoCool™ RF Ablation System

The OsteoCool™ RF Ablation System is comprised of the following main components which are described in Table 7-1 and Table 7-2:

Table 7-1: General Equipment

Products	Model/type	Product Description
OsteoCool™ RF Generator	OC01	Is a coaxial, bipolar RF Ablation platform. It is non-sterile and reusable. RF energy is applied to the subject according to the selected or configured settings. The procedure is automatically monitored, on a per-channel basis, for unexpected responses, which will cause messages to be displayed and RF energy delivery cessation, if appropriate.
OsteoCool™ Cart	OCA01	Is a non-sterile, reusable cart to mount the OsteoCool™ Radiofrequency Generator and OsteoCool™ Peristaltic Pump
OsteoCool™ Desk Stand	OCA02	Is a non-sterile, reusable desk stand to mount the OsteoCool™ Radiofrequency Generator and OsteoCool™ Peristaltic Pump
OsteoCool™ RF Pump Unit and Cable	OC02 – (OC02-R - replacement part only)	Is a non-sterile, reusable pump that circulates sterile water through a closed-loop system during OsteoCool™ radiofrequency (RF) ablation procedures. The OsteoCool™ Peristaltic Pump is suitable for continuous operation.
OsteoCool™ Connector Hub	OC04	Is a non-sterile, reusable cable which provides a path for delivery of radiofrequency (RF) energy and temperature signals to/from OsteoCool™ RF Ablation Probes, OsteoCool™ Independent Thermocouple Monitor, and OsteoCool™ RF Generator.

OsteoCool ™ Power Cord North America	OCE-NEMA515	Is the Power Cord for the OsteoCool Radiofrequency Generator
OsteoCool ™ Power Cord Italy	OC-CE12350	
OsteoCool ™Power Cord UK	OC-BS363	
OsteoCool ™Power Cord Swiss	OC-SEV1011	
OsteoCool ™Power Cord Europe	OCE-CEE7-INT	

Table 7-2: Consumable, Single Use Devices

Products	Model/type	Product Description
OsteoCool™ RF Ablation Single Probe Kit 4 different sizes	7mm: OCP107; OCP-107-INT 10mm: OCP110; OCP110-INT; 15mm: OCP115; OCP115-INT 20mm: OCP120; OCP120-INT	Is a sterile, single use device that delivers Radiofrequency (RF) energy to tissues. This energy is delivered through the probe, which is internally cooled. The single kit includes one OsteoCool™ RF Ablation Probe and one OsteoCool™ Tube Kit.
OsteoCool™ RF Ablation Dual Probe Kit 4 different sizes	7mm x2: OCP207; OCP207-INT 10mm x2: OCP210; OCP210-INT; 15mm; OCP215; OCP215-INT 20mm x2: OCP220; OCP220-INT	The double kit includes two OsteoCool™ RF Ablation Probes and two OsteoCool™ Tube Kits.
OsteoCool™ Independent Thermocouple 28 G (20G cannula)	OCN001; OCN001-INT	Allows for optional temperature monitoring around the ablation zones to ensure that there is no inadvertent damage to adjacent critical structures during the procedure.
OsteoCool™ Bone Access Kits	10G 090: OCN002 8G 090: OCN003 10G 095: OCN004 13G 100: OCN005	Is a sterile, single use device that is intended for percutaneous access to bone. OsteoCool™ Bone Access Kits include one Osteo Introducer (Cannula and Trocar Tip Stylet) and a color-marked OsteoCool Precision Drill.

7.2. Manufacturer

Medtronic Sofamor Danek, USA, Inc.
1800 Pyramid Place
Memphis, TN 38132
(901)396-3133 (Outside USA)
(800)933-2635 (USA)

7.3. Packaging

The OsteoCool™ RF Ablation Probe kit components are supplied sterile packed for single-use. Components should only be accepted if received by the hospital or surgeon with the factory packaging and labeling intact. Once the seal on the sterile package has been broken, the product should not be re-sterilized or reused. Labeling is specific to the geography and in accordance with local regulations.

7.4. Intended Population

The OsteoCool™ RF Ablation system is indicated in the US, EUR and CAN for patients with metastatic malignant lesions in a vertebral body, painful metastatic lesions involving bone (in the US, patients with metastatic lesions involving the bone must have failed or were not candidates for standard therapy) and benign bone tumors such as osteoid osteomas.

Standard therapy is defined per relevant medical society guidelines on treatment of metastatic lesions involving bone. For guidance, please refer to applicable medical society guidelines.

Candidates suitable for RF ablation procedures with the OsteoCool™ RF Ablation System include[29]

- *Patients experiencing significant pain from metastases involving bone*
- *Patients with localized pain resulting from not more than two sites of metastatic disease*
- *Patients that do not have evidence of impending fracture*

The OsteoCool™ RF Ablation System is contraindicated for the use in patients with heart pacemakers or other implanted electronic devices (Europe and Canada only), and for the use in vertebral body levels C1-C7.

All devices used in this study are commercially available and will be used within the intended approved indication as listed in the IFUs for the applicable countries/regions. Any future approved models may be used in the study if commercially available and if the modifications do not have the potential to affect the study results.

7.5. Equipment

The Medtronic OsteoCool™ RF Ablation system will be required for this study. The Generator verifies calibration integrity during the Power-On-Self-Test (POST). Maintenance is not required.

7.6. Product Use

The OsteoCool™ RF Ablation system will be used according to the standard surgical techniques. The operating surgeon should refer to the respective products' IFU for any corresponding product information prior to using the product.

While not required by the study protocol, the physician may decide that cementoplasty (i.e., Vertebroplasty or Kyphoplasty) is required after the ablation procedure. This information will be collected during the procedure and during any subsequent follow-up procedures.

7.7. Product Training Requirements

Physicians performing the RF ablation study procedure should have undergone standard product training by Medtronic on the proper use of its commercially available device prior to initiating the clinical study. Participating physicians must have performed ≥ 5 RF ablation procedures that involved either the bone and/or the vertebral body (not necessarily with the OsteoCool product) and ≥2 procedures with the Medtronic OsteoCool™ RF Ablation system to participate in the OPuS One clinical study.

7.8. Product Receipt and Tracking

This is a post-market study and the OsteoCool™ RF Ablation system used during the study is commercially available. Product receipt and tracking is not required as the devices used during the study are purchased through normal commercial channels.

7.9. Product Storage

Products should be stored per the institutions' standard procedures.

7.10. Product Return

Products should be disposed of or returned per the institutions' standard procedures.

7.11. Product Accountability

Product accountability is not required for this post-market study as the devices used during the study are purchased through normal commercial channels and maintained per the institutions' standard procedures.

8. Selection of Subjects

8.1. Study Population

Up to 250 subjects that meet eligibility and provide written informed consent will be enrolled into this study. Subjects will be enrolled in approximately 20 centers in the US, EUR, and CAN. Each center can enroll no more than 50 subjects without prior Medtronic approval.

8.2. Subject Enrollment

Patients planning to undergo OsteoCool RF ablation will be screened for eligibility to participate in the study. Subjects will be considered enrolled in the study once the informed consent form is signed; however, those who do not undergo the OsteoCool RF ablation procedure (e.g. RF therapy was not delivered) or did not meet the Inclusion/Exclusion criteria will be exited from the study.

8.3. Inclusion Criteria

In order to be eligible to participate in the study, a subject must meet all the following inclusion criteria:

1. *Candidate for OsteoCool RF ablation per the labeled indication applicable in their respective country/region*
2. A. Metastatic lesions targeted for treatment must be located in the thoracic and/or lumbar vertebral body(ies), periacetabulum, iliac crest, and/or sacrum OR benign bone tumors – no restrictions on location of lesion.
3. *Report worst pain score ≥4/10 at the target treatment site within the past 24 hours*
4. *Localized pain resulting from not more than two sites of metastatic disease*
5. *Have Karnofsky score ≥40 at enrollment (not applicable for subjects with benign bone tumors)*
6. *Willing and able to provide a signed and dated informed consent, comply with the study plan, follow up visits and phone calls*
7. *At least 18 years old at the time of informed consent*

8.4. Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participating in the study:

1. *A. Implanted with heart pacemaker or other implanted electronic device (Europe and Canada only)*
2. *Use of OsteoCool in vertebral body levels C1-C7*
3. *Multiple myeloma, solitary plasmacytoma, or primary malignant lesions in the index vertebra or bone.*
4. Active or incompletely treated local infection at the planned treatment site(s) and/or systemic infection
5. *Planned treatment site(s) accompanied by objective evidence of secondary radiculopathy or neurologic compromise*

6. *Planned treatment site(s) associated with spinal cord compression or canal compromise requiring decompression*
7. *Fractures due to prostatic cancer or other osteoblastic metastases to the spine. Metastatic lesions originating in the prostate that are osteolytic or of mixed origin are eligible for the study*
8. *Pregnant, breastfeeding, or plan to become pregnant during the study duration*
9. *Concurrent participation in another clinical study that may add additional safety risks and/or confound study results**
10. *Any condition that would interfere with the subject's ability to comply with study instructions or might confound the study interpretation*

*Subjects in concurrent studies can only be enrolled with permission from Medtronic. Please contact Medtronic's study manager to determine if the subject can be enrolled in both studies.

9. Study Procedures

9.1. Schedule of Events

The study schedule, procedures, and methods of assessment are defined in detail to enable compliance with the required activities, and to ensure that the resulting data meet the criteria for evaluability. See Figure 6-1 and Table 9-1 for visit requirements. A table listing protocol visit windows is presented in Table 9-2. The pertinent electronic Case Report Forms (eCRFs) along with the applicable source documentation will be completed for each subject.

9.1.1. Enrollment

Subjects are considered enrolled at the time the study-specific IC is signed.

9.1.2. Baseline

The Enrollment and Baseline visits can occur on the same day. Each subject must meet all of the inclusion criteria and no exclusion criteria to be eligible to continue participation in this study. Informed Consent must be signed prior to any study-related procedures.

The following information will be collected at the baseline visit:

- Verification of Inclusion/Exclusion criteria
- Pregnancy test for women of child-bearing potential
- Karnofsky Performance Scale (not applicable for subjects with benign bone tumors) (refer to section 9.6.3)
- Method by which focal pain was correlated with treatment site (e.g., imaging, physical examination)
- Demographics (refer to section 9.6.2)
- Collection of pre-treatment images (e.g., MRI, PET, etc.) relevant to the targeted site(s), – US and CAN only, if available
- Disease characteristics (refer to section 9.6.4)

- Prior and concomitant cancer and/or tumor treatments relevant to the targeted site(s), if applicable (refer to section 9.6.6)
- Prior and concomitant pain medications (refer to section 9.6.6)
- BPI – includes worst pain score in the past 24 hours at the target treatment site (refer to section 9.6.1)
- EQ-5D-5L (refer to section 9.7.9)
- EORTC QLQ-C15-PAL (not applicable for subjects with benign bone tumors) (refer to section 9.7.10)
- Reportable adverse events/device deficiencies/deviations (refer to section 11 and section 9.10)

Note: When possible, the follow up visits, questionnaires and data collection should be scheduled at least 72 hours after chemotherapy and/or radiation treatment.

9.1.3. OsteoCool Procedure (Day 0)

Enrollment, Baseline and RF ablation can occur on the same day. OsteoCool Procedure must occur ≤21 days after the baseline visit. Informed Consent must be signed prior to any study-related procedures.

The following information will be collected during the OsteoCool RF ablation procedure visit:

- Location of each treated site
- Concomitant cancer and/or tumor treatments, relevant to the target site(s), if applicable (refer to section 9.6.5)
- Concomitant pain medications (refer to section9.6.6)
- OsteoCool procedure data (per lesions treated)
- OsteoCool generator data uploads
- Use of Cementoplasty (i.e., Vertebroplasty or Kyphoplasty)
- PI assessment of local tumor control - optional
- Reportable adverse events/device deficiencies/deviations (refer to section 11 and section 9.10)

Follow the detailed procedures and instructions found in the applicable Instructions for use.

9.1.4. Prior to Discharge (Post RF Ablation)

Worst pain score at the treated site will be collected prior to discharge or within 12 hours of the procedure. Collection of post-treatment images (e.g., MRI, PET, etc.) at the treated site(s) (if available) in the US and CAN only. During this time, reportable adverse events, device deficiencies and deviations will also be collected.

9.1.5. Clinic Visits (3 days, 1 week, 1-, 3-, 6-, and 12-months post RF ablation)

Clinic visits will be scheduled 3 days, 1 week, 1-, 3-, 6- , and 12-months post RF ablation. The following information will be collected at these visits:

- Concomitant cancer and/or tumor treatments relevant to the treated site(s), if applicable (refer to section 9.6.5
- Concomitant pain medications (refer to section 9.6.6)

- BPI – includes worst pain score at the target treatment site in the past 24 hours (refer to section 9.6.1)
- PI assessment of local tumor control - optional
- EQ-5D-5L (refer to section 9.7.9)
- EORTC QLQ-C15-PAL (not applicable for subjects with benign bone tumors) (refer to section 9.7.10)
- Reportable adverse events/device deficiencies/deviations (refer to section 11 and section 9.10)
- Collection of post-treatment images (e.g., MRI, PET, etc.) at the treated site(s) (if available) – US and CAN only (refer to section 9.6.8)

Every attempt should be made to complete the required onsite clinic visit. However, if a subject is unable to complete an onsite visit, a phone follow-up visit eCRF can be completed by the Investigator/RC to obtain the required data elements.

Unscheduled visits will only be collected for visits conducted in the context of the study. The events required by each visit are presented in Table 9-1.

Table 9-1: Schedule of Events

Events	Enrollment Baseline[2]	OsteoCool Procedure (Day 0)[2]	Prior to Discharge or within 12 hours of the procedure	3 days, 1 week, 1-,3-,6-, and 12-Month Visits & unscheduled visits[5]	Phone eCRF (if needed)
Informed Consent Form[1]	X				
Eligibility (Inclusion/Exclusion Criteria)	X				
Pregnancy Test (Women of child-bearing potential)	X				
Demographics and Disease Characteristics	X				
Karnofsky Performance Scale[4]	X[4]				
OsteoCool / procedure details		X			
[redacted]	X	X	X	X	X
Generator data uploads (if available)		X			
PI assessment of local tumor control (optional)		X		X	
Concomitant cancer and/or tumor treatments, relevant to the target site(s)	X	X		X	X
Concomitant pain medications[3]	X	X		X	X
Worst pain score only			X		
BPI (Short Form) – includes worst pain score in the past 24 hours	X			X	X
EQ-5D-5L	X			X	X
EORTC-QLQ-C15-PAL[4]	X[4]			X[4]	
Deviations	X	X	X	X	X
Event Review (AE/DD)	X	X	X	X	X

1) Informed consent must be obtained prior to performing any study-specific procedures.
2) Baseline Visit, Enrollment Visit and procedure can occur on the same day. Baseline visit shall be performed ≤ 21 days before the OsteoCool procedure
3) Oral narcotics within past 24 hours
4) Not applicable for subjects with benign bone tumors
5) Unscheduled visits will only be collected for visits conducted in the context of the study

Table 9-2: Protocol Visit Windows*

Visit	Visit ranges
Enrollment/Baseline	NA
Procedure (Day 0)	≤21 days after Baseline visit
Discharge	Prior to hospital discharge or within 12 hours of the procedure
Monthly Clinic Visits	3 Days: 3 days ± 2 Days after Day 0 1 week: 7 days± 2 Days after Day 0 1-Month Visit: 30 days ± 15 Days after Day 0 3-Month Visit: 90 days ±30 days after Day 0 6 Month Visit: 180 days ±59 days after Day 0 12 Month Visit: 365 days ± 90 days after Day 0

*Every attempt should be made to complete the required onsite clinic visit. However, if a subject is unable to complete an onsite follow-up visit due to physical circumstances, a Phone follow-up visit eCRF can be completed by the Investigator/RC to obtain the required data elements.

9.2. Subject Screening

Subjects may be recruited through the investigator's practice and referring physicians.

Potential subjects may be identified through chart reviews or as new or existing patients. If subjects are recruited from outside the investigator's practice, sites are to ensure that appropriate release for access to the subject's records (paper and/or electronic) is obtained. Any subject recruitment materials disseminated to subjects (advertisements, handouts, posters, and social media) must be approved by the IRB/EC prior to use.

Recruited subjects will be screened by the Principal Investigator or authorized site personnel by reviewing the study's inclusion and exclusion criteria. All subjects must be consented in accordance with the protocol prior to any study-specific procedures.

A screening log will be completed by the site to maintain a cumulative log of all screened subjects with reason for screening failure when applicable and provided to Medtronic upon request.

The Investigator will maintain a listing of all subjects enrolled in the clinical investigation and a subject identification code linked to each subject's name.

9.3. Subject Consent

The informed consent process will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and 21 Code of Federal Regulations (CFR)§50 Protection of Human Subjects (US only).

Prior to entering the study, the Principal Investigator or delegated designee will explain to each subject the purpose and nature of the study, procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment. Subjects will be given a copy of the IRB/EC-approved IC and will have time to review the document and

to ask questions and will be informed of their right to withdraw from the study at any time without prejudice; ICs will be provided in a language understandable to the subject. After this explanation and before any study-specific procedures have been performed, the subject will voluntarily sign and date the IC. In Europe, the PI or delegate must also sign the IC. Prior to participation in the study, the subject will receive a copy of the signed and dated informed consent and any other written information provided to the subject.

The Principal Investigator or qualified (delegated) designee will document the informed consent process, including the date of consent and name of the person conducting the consent process in the subject's medical record. If the Baseline visit, Enrollment Visit and procedure are done on the same day, documentation should indicate that the IC was signed before any study related procedures. A copy of the signed IC will also be placed in the subject's medical record.

Amendments to the IC can be obtained by other methods if the subject is unable to return due to illness or logistics. The IC should be sent to the subject by mail, fax, or email and then a discussion should occur by phone. The subject must be able to refer to the written document during the phone discussion. The subject can sign/date the IC and return it by mail, fax, scanning/emailing through a secure account, or posting it to a secure internet address. Alternatively, the subject may bring the signed and dated consent form to his/her next visit to the clinical site or mail it to the clinical investigator. The subject must receive a copy of the consent form. This process should be documented in the subject's medical record.

9.4. Randomization and Treatment Assignment

Randomization is not applicable for this study.

9.5. Medication Compliance

Medication compliance is not applicable for this study.

9.6. Assessment of Efficacy

9.6.1. Brief Pain Inventory (BPI)[30,31]

The Brief Pain Inventory short form is a 9 item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patient is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 11 point scale.

The worst pain question in the BPI will be used to evaluate the pain severity:

> *Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours (circle only one number, 0-10). No pain = 0, Pain as bad as you can imagine = 10*

The BPI pain interference is typically scored as the mean of the seven interference items (general activity, mood, walking ability, normal work, relations with other people, sleeping, and enjoyment of life). The mean can be used if more than 50% or 4/7 of the total items has been completed.

The general pain question (Question #1), pain map (Question #2) and the medication question (Question #7) will not be used in this study. The removal of these questions does not affect the validity of the questionnaire and was approved by the BPI author Charles S. Cleeland, PHD

The BPI can be completed by the subject, by in-person interview or by phone interview by the Principal Investigator or qualified (delegated) designee.

9.6.2. Cancer Medical History and Demographics

Relevant cancer medical history and demographic information will be collected at the Baseline visit and reported on the applicable eCRFs.

9.6.3. Karnofsky Performance Scale (KPS)[32]

The Karnofsky Performance Scale Index classifies patients as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. Functional status is assessed by the physician. The KPS ranges from 100 to 0, where 100 is “perfect” health and 0 is death. The lower the Karnofsky score, the worse the survival prognosis for most serious illnesses.

Not applicable for subjects with benign bone tumors.

9.6.4. Disease Characteristics

- *Primary cancer type and year of diagnosis*
- *Histology (if available)*
- *Metastases and/or tumor site information – location, characteristics*
- *Imaging (if available), for US and CAN subject/sites only*

9.6.5. Prior and Concomitant Cancer and/or Tumor Treatments

Most recent treatments relevant to the treated/target site(s):

- *Chemotherapy*
- *Radiation therapy*
- *Immunotherapy*
- *Antibody therapy*
- *Surgical procedures for cancer and/or tumor treatment including other ablative therapies*
- *Other, specify*

9.6.6. Prior and Concomitant Medications

There are no restrictions to prior or concomitant medications before or during the study. The specific concomitant medications listed below should be documented as concomitant medications and will be updated at each visit:

- ***Osteoporosis medication(s):*** *Antiresorptive medications (e.g., bisphosphonates, parathyroid hormone (PTH), calcitonin), calcium, and vitamin D.*
- ***Steroid(s):*** *any steroid use, including steroid inhalers*
- ***Oral narcotics in last 24 hours.*** *This information will be converted to oral morphine equivalent dose (OMED) (including transdermal patches)*

9.6.7. Response Rate[33]

Response rate at 3 months post RF ablation is defined in Table 9-3. Complete Response (CR) and Partial Response (PR) will be considered as treatment response. Pain Progression (PP) and Indeterminate Response (IR) will be considered as treatment non-response.

Table 9-3: Composite Endpoint

Treatment Response	Complete Response (CR)	A worst pain score of 0 with no concomitant increase in daily oral morphine equivalent dose (OMED) within the last 24 hours
	Partial Response (PR)	Pain reduction of 2 or more on a scale of 0-10 without increase in OMED, or OMED reduction of 25% in the last 24 hours or more from baseline without an increase in pain.
Treatment Non-response	Pain Progression (PP)	Increase in pain score of 2 or more above baseline worst pain score with stable OMED, or an increase of 25% or more in OMED within the last 24 hours compared with baseline with the worst pain score stable or 1 point above baseline.
	Indeterminate Response (IR)	Any response that is not captured by the complete response, partial response, or pain progression definitions

9.6.8. [redacted]

[redacted]

9.7. Assessment of Quality of Life Measures

Subjects and/or Principal Investigator or qualified (delegated) designee (if completed by phone) will complete the study questionnaires confidentially on paper forms and this data will be entered into the OC RDC system by site personnel. The patient can consult with the site for direction on how to complete the questionnaires. Questionnaires should be completed prior to the meeting with the investigator. Site personnel should review all forms for completeness.

9.7.9. European Quality of Life – Five Dimensions (EQ-5D-5L)[34]

The European Quality of Life – Five Dimensions (EQ-5D), version 5L, is a standardized measure of health status developed by the EuroQol Group and a widely used validated tool to determine health-related quality of life. The EQ-5D-5L consists of two sections, the descriptive system and the EQ visual analogue scale (EQ VAS).

The EQ-5D descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of severity: no problems, slight problems, moderate problems, severe problems, extreme problems. The subjects are asked to indicate his/her health state by selecting the most appropriate statement in each of the 5 dimensions.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents.

The EQ-5D can be completed by the subject, in-person interview, or by phone interview by the Principal Investigator or qualified (delegated) designee.

9.7.10. European Organization for Research and Treatment (EORTC QLQ-C15-PAL) [35]

The EORTC QLQ-C15-PAL is a module developed to measure the QOL in patients with bone metastases. It includes four subscales: painful sites, pain characteristics, functional interference, and psychosocial aspects. This questionnaire is not applicable for subjects with benign bone tumors.

The EORTC QLQ-C15-PAL must be completed by the subject.

9.8. Assessment of Safety

Subjects will be assessed for potential reportable adverse events and device deficiencies (as defined in Section 11) at each study visit.

9.9. Recording Data

The Investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs must be consistent with the source documents, and discrepancies need to be justified in a documented rationale, signed and dated by the Investigator, and filed in the subject medical file or appropriate location.

All source data entered in the eCRFs should be located in the subject's medical records/source document (electronic or paper), (e.g., hospital records, surgery reports, x-rays, MRIs, CTs, or any other material that contains original information used for data collection including the documentation of AEs and study source document completed by the Investigator or site staff). Subject completed questionnaires as well as data collected during subject phone calls will be considered as source data.

This study will be conducted using a remote data capture system. The Oracle Clinical Remote Data Capture (RDC) system allows the study centers to enter study data into the sponsor's database over a secure internet connection. Required data will be taken from source documents and directly entered into the study database by authorized site personnel in accordance with applicable regulations.

If the subject is unable to return to the investigational site for their scheduled clinic visit, the study site can contact the subject and collect the following data by phone using the phone visit source document worksheet:

- *BPI – conducted by phone*
- *EQ-5D-5L – phone version*
- *Oral narcotic intake in the past 24 hours*
- *Concomitant procedures/treatments*
- *Reportable adverse events and/or device deficiencies*

The Principal or Sub-Investigator, or an individual delegated by the Principal Investigator on the Delegation of Authority and Signature Form, is responsible for documenting and entering data for the study on the eCRFs. The Principal Investigator or delegated Sub-Investigator is required to approve all data on CRFs via electronic signature.

9.10. Deviation Handling

Protocol deviations are digressions from the written protocol defined as an event where the clinical investigator or site personnel did not conduct protocol-required procedures according to the study protocol. Protocol deviations are to be preapproved by Medtronic study personnel and the IRB/EC (as required) unless the deviation is necessary to protect the health, safety, or welfare of a subject in an emergency situation. The investigator or delegated site personnel should immediately contact the designated Medtronic study personnel to discuss the impact of the potential deviation; prior approval of deviations should be documented. Prior approval is generally not required if the deviation is due to an emergency circumstance or an unforeseen circumstance that is beyond the investigator's control; however, these deviations should be reported to Medtronic and the IRB/EC (as required) after site personnel become aware of the deviation. All protocol deviations must be reported on the Protocol Deviation eCRF after the site's awareness of the deviation.

The sponsor may choose to terminate the study at a site for failure to follow the written protocol and investigator agreement. If this occurs, the Investigator and IRB/EC will be notified in writing of the reasons for the termination.

9.11. Subject Withdrawal or Discontinuation

Subjects are free to voluntarily withdraw from the study at any time and for any reason. The investigator can withdraw a subject from the study at any time and for any reason. Withdrawn or exited subjects will be followed under normal medical practice.

Examples of reasons for subject discontinuation include, but are not limited to, those listed below:

- If the subject does not meet all eligibility criteria
- Subject death
- Subject lost to follow-up
- Subject voluntarily withdraws from the study
- Subject becomes pregnant
- OsteoCool RF ablation was not performed or was aborted and RF therapy was not delivered
- Investigator terminates the subject's participation in the study (e.g., failure to return for scheduled visits, failure to comply with the protocol)
- Any clinical laboratory abnormality, inter-current illness, or other medical condition or situation occurs such that continued study participation would not be in the best interest of the subject.
- Normal study completion. After the completion of the 12 Month follow-up visit, a Study Exit eCRF should be completed to document normal study completion.
- Sponsor terminates study early due to low enrollments and/or attrition

Study Exit eCRF must be completed on all enrolled subjects. Detailed notes as to why the subject was withdrawn from the study (e.g., discomfort, lack of efficacy, questionnaires too burdensome, lost to follow-up, death) should be included. There will be no further medical care provided under the study after a subject exits.

If the RF ablation was not performed, aborted or RF therapy was not delivered, the subject will be discontinued from the study and a Study Exit eCRF should be completed. Withdrawn subjects will not be replaced.

When a subject is withdrawn from the study between scheduled visits, complete the unscheduled visit eCRF (with the exception of lost to follow-up and death) as well as the Study Exit eCRF.

Prior to deeming a subject is lost to follow-up, telephone calls must be documented in the subject's medical record. If a minimum of three attempts to contact the subject have failed (e.g. phone and mailed letter), and no response is received, the site should exit the subject and complete the Study Exit eCRF.

If early termination is due to death related to the device, procedure and/or therapy related adverse event, the Adverse Event eCRF should be completed as well as the Study Exit eCRF. In case of death, the Investigator should maintain original source documents pertaining to the death of any subject (e.g., death certificate; autopsy report, if done; hospital death summary if subject died in hospital, if available).

10. Risks and Benefits

10.1. Potential Risks

There are no known incremental risks associated with participating in this study.

10.2. Risks Outlined in the Instructions for Use (IFU)

Refer to the appropriate Instructions for Use (IFU) for the OsteoCool™ RF Ablation system components for updated list on contraindications, precautions, warnings, adverse events, directions for use and other product specific details.

10.2.1. OsteoCool™ RF Ablation Probe Kit

Indications for Use (US)[29]:

The OsteoCool™ RF Ablation Probe Kit, in combination with other components of the OsteoCool™ RF Ablation System, is intended for:

- Palliative treatment in spinal procedures by ablation of metastatic malignant lesions in a vertebral body.
- Coagulation and ablation of tissue in bone during surgical procedures including palliation of pain associated with metastatic lesions involving bone in patients who have failed or are not candidates for standard therapy.
- Ablation of benign bone tumors such as osteoid osteoma.

Indications for EUR and CAN[36]:

The OsteoCool™ RF Ablation Probe Kit, in combination with other components of the OsteoCool™ RF Ablation System, is intended for ablation of benign bone tumors such as osteoid osteoma and palliative treatment by ablation of metastatic malignant lesions involving bone, including the vertebral body.

Contraindications[29,36]:

- Use of the OsteoCool™ RF Ablation System is contraindicated in patients with heart pacemakers or other electronic device implants. (Europe and Canada only)
- Use of the OsteoCool™ RF Ablation System device is contraindicated in vertebral body levels C1-C7.

Warnings[29,36]:

- Do not use in patients who have electronic implants such as cardiac pacemakers without first consulting a qualified professional (e.g., cardiologist). A possible hazard exists because interference with the action of the electronic implant may occur, or the implant may be damaged. (US only)
- The OsteoCool™ RF Ablation Probe Kit contains single use devices. They should not be re-sterilized or re-used. Reuse can cause the patient injury and/or the communication of infectious disease(s) from one patient to another.
- Take appropriate precautions for patients with blood coagulation disorders, anticoagulant use, neurological deficit, or systemic infection or local infection in area of the procedure.

- The procedure is to be performed with minimal to moderate sedation to allow the patient to remain in a communicative state for patient feedback.
- Adequate measures must be taken to minimize x-ray exposure while using fluoroscopy. This exposure can result in acute radiation injury as well as increased risk for somatic and genetic effects.
- Do not modify the equipment as this may compromise safety and efficacy.
- When the OsteoCool™ RF Generator is activated, electrical fields may interfere with other electrical medical equipment.
- During power delivery, the patient should not be allowed to come in contact with grounded metal surfaces.
- Discontinue use if inaccurate, erratic, or sluggish temperature readings are observed. Use of damaged equipment may cause patient injury.
- For safe use of the OsteoCool™ RF Ablation System, the physician should have specific training, experience, and through familiarity with the use and application of this product.
- Do not ablate in painful osteoporotic vertebra without tumor.
- Do not use the device in fractures due to prostatic cancer or other osteoblastic metastases to the spine.
- Do not use the products in dense (sclerotic) bone including traumatic high energy fracture as device damage resulting in patient injury may occur.
- [US only]Do not use this device in patients without metastatic malignant lesions in bone or in the vertebral body.
- [EU and CAN only) Do not use this device in patients without osteoid osteoma or metastatic malignant lesions in bone or in the vertebral body.
- When using this device in the vertebral body, do not use this device in patients with multiple myeloma, solitary plasmacytoma, or primary malignant lesions in the index vertebra.
- Do not use this device in more than one vertebral body.
- Do not touch the electrode tip while power is being applied.
- Do not withdraw the OsteoCool™ RF Ablation Probe while power is being applied to ablate lesions.
- Use standard electrosurgical cautions when using the OsteoCool™ RF Ablation System in the vicinity of nerves and nerve roots.
- Ablation must be performed under fluoroscopic guidance. Do not perform ablation without imaging as it will result in severe injury to the patient.
- When using this device in the vertebral body, the OsteoCool™ RF Ablation Probe must be positioned within the vertebral body such that when ablation is performed per the thermal distribution graphs, nerves and nerve roots are beyond the ablation zone. Failure to follow the thermal distribution graphs will result in severe injury to the patient.
- Precautions during ablation near organ surface or near vasculature – Due to the non-homogenous conduction and convection of heat in this anatomy, shapes of ablations performed on tissue that is near the organ surface or near vasculature may not be spherical. Careful planning should be done for targets that require ablation in these locations.
- Any application or procedure that alters tissue perfusion and affects temperature elevation should be monitored carefully.

- High power settings can cause local desiccation of tissue, which can impede the ability to produce expected ablations. Set power as low as possible for intended purpose. Follow manufacturer's guidelines of time at temperature for ablation generation. If the recommended times and temperatures are not achieved there can be no assurance that the desired ablation volume has been created. Standard techniques for evaluation (e.g. CT or MRI) should be used to determine the actual extent of all ablations.
- It is important to carefully evaluate all candidates for this procedure for evidence of impending fracture, particularly in weight-bearing bone. Do not perform RF ablation of metastases in weight-bearing bone with evidence of impending fracture. Note: Pathologic fracture is more prevalent and serious in long bone.
- It is important to carefully evaluate all candidates for this procedure for proximity of the metastasis to critical structures. Ensure that device placement is at least 1cm away from the structures not intended for ablation. Proximity to nerve structures is particularly critical. Serious complications such as incontinence can occur if these critical structures are damaged during the RF ablation procedure.
- The durability of pain relief after using this device to ablate painful bone metastases has not been established.

Precautions[29,36]**:**

- The OsteoCool™ Tube Kit should never be disconnected from the OsteoCool™ RF Ablation Probe when RF delivery is in progress. The lumen of the tube kit should not be obstructed in any way during the procedure, as this will stop cooling of the probe.
- Disconnect the OsteoCool™ RF Ablation Probe by pulling the connector, not the cable.
- Handle the OsteoCool™ RF Ablation Probe safely when it is in use due to electric currents and the hot tip.
- Do not bend the OsteoCool™ RF Ablation Probe as this may damage the insulation.
- Do not remove or withdraw the OsteoCool™ RF Ablation Probe while energy is being delivered to ablate lesions.
- While inserting the OsteoCool™ RF Ablation Probe through the Introducer watch the fluoroscope for any buckling. Do not attempt to further insert the probe if any buckling is observed or significant resistance is felt.
- Do not move the Introducer when the OsteoCool™ RF Ablation Probe is in it. If repositioning is needed, retract the probe from the introducer and then reposition the introducer with the stylet inserted.
- The physician must determine, assess, and communicate to each individual patient all foreseeable risks of the RF procedure.
- The "Temperature" displayed on the generator while in "Ablate" refers to the cooled electrode temperature and not the hottest tissue temperature.

Adverse Events[29,36]**:**

The OsteoCool™ RF Ablation Probe Kit is used with other components of the OsteoCool™ RF Ablation System in RF lesion procedures. Adverse events associated with the use of this device are similar to those indicated for medicated and anesthetic methods utilized in other surgical procedures.

- As a consequence of electrosurgery, damage to surrounding tissue through iatrogenic injury could occur.
- Nerve injury including thermal injury, puncture of the spinal cord or nerve roots potentially results in radiculopathy, paresis, and paralysis.
- Pulmonary embolism
- Hemothorax or pneumothorax
- Infection including deep or superficial wound infection
- Unintended puncture wound including vascular puncture and dural tear
- Hemorrhage
- Hematoma
- Pain

10.2.2. OsteoCool Bone Access Kit[37]

Warnings:

Breakage of the device may require intervention or retrieval.

Precautions:

The OsteoCool™ Bone Access Kit is a single use device intended to contact body tissues. Do not reuse, reprocess, or resterilize. Reusing these devices carries the risk of contamination and may cause patient infection or cross-infection, regardless of the cleaning and resterilization methods. There is also an increased risk of the deterioration of the devices performance due to the reprocessing steps, which may lead to patient injury or death.

- It is important to read the Instructions for Use and these precautions carefully prior to device operation.
- Use the devices prior to the use by date noted on the package.
- Do not use if package is opened or damaged because product integrity including sterility may be compromised.
- Do not use damaged products. Before use, inspect all system components and packaging to verify no damage has occurred.
- Do not use this product if you have not been properly trained in its use. Physicians using the devices should be familiar with the physiology and pathology of the selected anatomy, and be trained in the performance of the chosen surgical technique.
- Components of each system should be manipulated only while under fluoroscopic observation with radiographic equipment that provides high quality images.
- Access to the vertebral body via the pedicle requires a minimum pedicle width of 5mm. Insertion of the instruments requires specific knowledge of the dimensions of the site of insertion to bone as assessed by MRI, CT, or other imaging method.
- Never use electric or other powered instruments/devices in conjunction with the OsteoCool™ Bone Access Kit. Use only manual power when using the OsteoCool™ Bone Access Kit.

- Do not resterilize and/or reuse. The OsteoCool™ Bone Access Kit is for single use only. Reconditioning, refurbishing, repair, modification, or resterilization of the device to enable further use is expressly prohibited.

PHYSICIAN NOTE: Although the physician is the learned intermediary between the company and the patient, the important medical information given in this document should be conveyed to the patient.

Adverse Events:

Adverse events potentially associated with use of the device include:

- Nerve injury including puncture of the spinal cord or nerve roots potentially resulting in radiculopathy, paresis, or paralysis
- Embolism of fat, thrombus, or other materials resulting in symptomatic pulmonary embolism or other clinical sequelae
- Hemothorax or pneumothorax
- Deep or superficial wound infection
- Unintended puncture wounds including vascular puncture and dural tear
- Bleeding or hemorrhage
- Hematoma
- Pain

10.3. Risk of Imaging/Radiation

Subjects will be exposed to a small amount of radiation that they will receive during the study. The amount of this radiation cannot be determined in advance. For example, during the initial procedure, fluoroscopy or CT may be used according to standard of care at the site or an Investigator may order pre-operative or post-operative x-ray films or CT scans to assess the lesions/tumors. These images are routine and according to the standard of care; therefore no additional radiation risk is associated with participation in this clinical study.

10.4. Potential Benefits

An analysis of radiofrequency tumor ablation literature concluded that, the use of ablation techniques, particularly radiofrequency energy-based methodologies, have proven to be effective in providing significant pain relief in the majority of subjects, with minimal failures or complications reported.[38, 23, 39]

There may be no direct benefits of study participation. However, subject participants will undergo an enhanced level of clinical scrutiny compared to routine clinical care, which may provide some indirect health benefits. Participation contributes to expand the knowledge base with respect to the treatment of bone metastasis in the spine.

10.5. Risk-Benefit Rationale

Participation in this study will not expose the subject to greater risks than if he/she were receiving OsteoCool RF Ablation system outside of the study. There might be other discomforts and risks related to OsteoCool RF Ablation system and/or this study that are not foreseen at this time.

The risks associated with OsteoCool RF Ablation system are minimized in this study by selecting only qualified Investigators experienced in RF ablation procedures of the vertebral body and/or bone, selecting an appropriate patient population via inclusion/exclusion screening, and monitoring subject functional progress and events reported for this study. The review and minimization of the potential risks to the patient and the potential benefits to the patient support the conduct of this study.

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

Any adverse event meeting the definition of: device, therapy, and/or procedure related as well as all device deficiencies will be considered reportable for this study. Medtronic will classify each adverse event according to ISO 14155:2011. Adverse events and device deficiencies are defined as follows:

Table 11-1: Definitions

Term	General
Adverse Event (AE) (ISO14155:2011 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE) (ISO14155:2011 3.1)	Adverse event related to the use of an investigational medical device. Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Device Deficiency (DD) (ISO 14155:2011 3.15; ISO 14155:2011 3.27; ISO 14155:2011 3.43;)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note: Device deficiencies include malfunctions, use errors, and inadequate labeling. ▪ Malfunctions: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigational Plan (CIP) ▪ Use Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user Note 1: Use error includes slips, lapses, and mistakes. Note2: An unexpected physiological response of the subject does not in itself constitute a use error.

SERIOUSNESS	
Serious Adverse Event (SAE) (ISO 14155:2011 3.37)	An adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in: 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect. Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) (ISO 14155:2011 3.36)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2011 3.42)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
RELATEDNESS	
Relationship of Adverse Events	The relationship of the adverse event to the study treatment (device, therapy and/or procedure) will be described by the investigator using the following terms: • *Not related* • *Unlikely* • *Possible* • *Probable* • *Causal relationship*

Severity	
Severity of the Adverse Events	The investigator's assessment of severity must be provided for AEs reported for this study. The following classifications are to be used to classify the severity of the reported safety event: **Mild**: The AE is noticeable to the patient but does not interfere with routine activity. **Moderate**: The AE interferes with routine activity but responds to symptomatic therapy or rest. **Severe**: The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy. All hospital admissions or emergency room (ER) visits are graded at least as severe.
SIR AE Classification	
Society of Interventional Radiology (SIR) Classification System for Complications by Outcome	Minor Complications A. No therapy, no consequence B. Nominal therapy, no consequence; includes overnight admission for observation only. Major Complications C. Require therapy, minor hospitalization (<48 hours) D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours) E. Permanent adverse sequelae F. Death.

For the OPuS One clinical study, cement extravasations are reportable if:

1. The extravasation is >15 mm; or
2. If the extravasation of any volume of cement results in any adverse event (e.g., spinal cord compression, nerve injury, embolic event).

Extravasation that does not result in a negative clinical event will not be considered as an adverse event for this study.

11.2. Reporting of Adverse Events

Any adverse event meeting the definition of device, therapy and/or procedure related as well as all device deficiencies that occur from enrollment through subject discontinuation from the study will be collected.

The following categories of adverse events will be collected for this study from enrollment to the end of the study:

- All device, therapy and/or procedure-related adverse events including events related to:
  - The device components and/or procedure (Bone Access Kit, Probe, generator, etc.)
  - Surgery or anesthesia regarding the initial or repeat procedure

In addition, all device deficiencies reported during the study will be collected. Worsening of pain symptoms at the treated site will be collected as part of the efficacy measures and are not considered a reportable adverse event unless the nature, severity, duration and or frequency of pain at that location has changed. All reportable adverse events will be classified using the following responsibility matrix:

Table 11-2: Event Classification Responsibilities

What is Classified	Who Classifies	Classification Parameters
Relatedness	Investigator CEC (deaths only)	Procedure related Device/therapy related
USADE potential	Medtronic	USADE
SIR Classification	Medtronic	SIR AE Classification
Seriousness	Investigator	SAE/SADE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Medtronic	MedDRA term assigned based on the data provided by investigator

All reportable events must be recorded in the subject's medical record and on the Adverse Event and/or Device Deficiency eCRF and promptly reported to Medtronic. IRB/EC reporting must be completed in accordance with the policies of the governing IRB/EC. Competent Authority reporting should be in accordance with applicable local regulations.

It is the responsibility of the Investigator to identify the occurrence of reportable adverse events and device deficiencies and to ensure the required information is accurately documented on the eCRF. Reports of adverse events and device deficiencies will include the following information, at a minimum:

- *Date of event*
- *Diagnosis or description of the event*
- *Assessment of the seriousness and relationship to the product(s) under study*
- *Treatment*
- *Outcome and date of resolution*

The clinical course of each adverse event must be followed until resolution or subject discontinuation from the study, whichever comes first. "Ongoing" adverse events and device deficiencies must be assessed at each protocol required visit, and new or updated information must be documented on the Adverse Event and/or Device Deficiency eCRF and promptly reported to Medtronic and if applicable to the IRB/EC.

If necessary, the Investigator may report to the sponsor initially by telephone or email and follow-up with completed eCRFs and, if possible, copies of source documentation regarding the event (e.g., physician/nurse notes or summaries).

Medtronic study personnel will promptly review all reported adverse events and device deficiencies and if necessary request clarification and/or additional information from the Investigator. If Medtronic disagrees with the Investigator's assessment of the adverse event relationship to the device and/or procedure, Medtronic study personnel will document the disagreement and report or ensure reporting

of both opinions to the IRB/EC as necessary. All reported adverse events and device deficiencies will be reviewed by a Medtronic Medical Advisor to ensure consistent reporting.

11.3. Not Reportable Events

Examples of events that are not reportable as adverse events for this study are:

- *Inability to successfully perform the procedure, unless injury occurs.*
- *Lack of pain relief or a return to baseline pain level (change in pain will be assessed as the efficacy objective).*
- *A documented pre-existing condition unless there is a worsening of the nature, severity, duration, or frequency of that condition if it meets the defined criteria in Section 11.2.*
- *Planned medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion, cosmetic elective surgery); however, the condition leading to the procedures might be a reportable event if it meets the defined criteria in Section 11.2.*

Table 11-3 provides a list of expected surgical adverse events. An expected surgical event will not be considered reportable unless it worsens or is present outside the stated timeframe post-procedure.

Table 11-3: Expected Surgical Adverse Events and Durations

Event description	Time frame after the surgical procedure
Anesthesia-related nausea/vomiting	24 hours
Low-grade fever (<100ºF or < 37.8ºC)	48 hours
Mild to moderate bruising / ecchymosis	7 days
Seroma	72 hours
Sleep problems (insomnia)	72 hours

11.4. Device Deficiencies

A device deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling. All device deficiencies must be documented and submitted to Medtronic on the Device Deficiency eCRF. In addition, the Investigator must also determine and document on the eCRF device deficiencies that did not lead to adverse event but could have led to a serious adverse device effect:

- *if either suitable action had not been taken,*
- *if intervention had not been made, or*
- *if circumstances had been less fortunate*
- *Refer to Table 14-1 for Investigator reporting timelines for device deficiencies.*

11.5. Reporting Serious Adverse Device Effects, and Device Deficiencies to Medtronic

Reporting timelines can be found in Table 14-1. If necessary, the Investigator may report the event to Medtronic or its designee initially by telephone or email and follow-up with completed Adverse Event and/or Device Deficiency eCRFs and, if possible, copies of source documentation regarding the event (e.g., physician/nurse notes or summaries) should also be provided to Medtronic.

24-hour Medtronic contact information for reporting SADEs/DD:
Phone: +1-763-526-8178
Email: rs.opus@medtronic.com.

11.6. Deaths

All subject deaths must be reported to Medtronic and the IRB/EC as soon as possible, but **no more than 5 working days** after learning of a subject's death, regardless of whether or not the death is related to the device system or therapy. The Investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the device system, therapy, and/or procedure. If the death is evaluated as device, therapy and/or procedure related and unanticipated, the event will be reported as a USADE by Medtronic or its designee to the appropriate regulatory agencies.

The principal investigator should provide as much of the following supporting documentation as possible for deaths:

- *Death certificate*
- *Death summary/hospital records, if allowed by state/local law*
- *Autopsy report, if allowed by state/local law*

All device system components that were being used at the time of the death should be returned to Medtronic for analysis, if applicable. Any subject death related to the device/procedure and/or therapy will be reported on the Adverse Event and Study Exit eCRFs. If limited information is known, the Study Exit eCRF must be completed with available information as soon as possible. As information becomes available, the Study Exit eCRF will be updated and/or an Adverse Event eCRF may be required if the death was later determined to be related to the device, procedure and/or therapy. If the death occurs at a location remote from the study site, it is the study site's responsibility to make every attempt to retrieve all pertinent information related to the subject's death and submit the investigator's death summary of the known events surrounding the death to Medtronic or its designee.

12. Data Review Committees

This study will utilize an independent Clinical Events Committee (CEC) to adjudicate deaths to determine the relationship of the death to the device, procedure and/or therapy.

The CEC may request clarification and/or additional information from the principal investigator who reported the event. If the conclusion of the review differs from the principal investigator's assessment, both opinions will be reported back to the investigator and noted in the final study report.

13. Statistical Design and Methods

13.1. General Statistical Considerations

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package (e.g., SAS version 9.4 or higher) will be used to analyze the study results.

The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

13.1.1. Study Sample Size Justification

The sample size calculations were performed using PASS 11 statistical software. (PASS 11 v. 11.0.7, Hintze J). Details of the sample size calculations are provided in the primary objective section.

The primary objective is to demonstrate an improvement from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions involving only the vertebral body. A sample size of 35 subjects successfully treated and completing the pain assessment at 3 months is expected to provide results that will be considered relevant to clinicians, as well as provide acceptable power to test the primary objective. After accounting for the attrition from treatment through the pain assessment at 3 months, 52 subjects are required to be treated with the OsteoCool™ RF Ablation system.

Sample size requirements will only be calculated for the primary objective. There are no sample size requirements for the secondary objective and the additional objectives.

Enrollment Sample Size

The study size will be 250 enrolled subjects. The goal is 100 with metastatic lesions involving only the vertebral body, 100 with metastatic lesions outside the vertebral body, and 50 with benign bone tumors. The increased sample size will allow for richer safety reporting and long-term follow-up.

13.1.2. Description of Baseline Variables

Baseline variables representing subject clinical characteristics will be presented.

13.1.3. Center Pooling

Throughout the study, efforts will be made to ensure consistency among investigative centers in selection of subjects and conduct of the study procedures. Training on the protocol and programming

procedures will be done for all sponsor and center staff involved in this study. Center monitoring will also help ensure consistency.

Due to the relatively small number of subjects expected at each center, there is no plan to use statistical methods to test for a difference among centers. There is no a priori plan to analyze the primary and secondary objectives by study center.

There is no a priori plan to exclude any centers from the analysis.

For the overall study size of 250, each center can contribute no more than 50 subjects (from both subject cohorts combined) without prior Medtronic approval.

13.1.4. Special Considerations

Subject Cohorts

There will be two subject cohorts, which will be used to separate the subjects to be analyzed in the primary objective versus the secondary objective.

> ***Primary objective cohort:*** subjects with metastatic lesions involving the vertebral body only
>
> ***Secondary objectives cohort:*** subjects with metastatic lesions and benign bone tumors outside the vertebral body. This includes subjects with a combination of lesions involving the vertebral body and outside the vertebral body. This cohort may get divided further depending on treatment site (for example: non-vertebral bone, benign bone tumors, combinations).

At the time of treatment with the OsteoCool™ RF Ablation system, subjects will get assigned to one of the two cohorts depending on the lesion type(s) treated. The two cohorts encompass the entire set of treated subjects, and are mutually exclusive.

Analysis Populations

There are 3 analysis populations:

The ***Enrolled*** will include all enrolled subjects and will be used in the safety measures.

The populations of study subjects to be included in the efficacy analyses (primary objective, secondary objective, and additional measures) are described below.

> ***Treated:*** The Treated population will be defined as all subjects who are successfully treated with the OsteoCool™ RF Ablation system. This is similar to a Full Analysis Set.
>
> ***Completers:*** The Completers population will be defined as the subset of ***Treated*** subjects who provided endpoint data at the 3-Month Visit. The Completers population will be a subset of the Treated population. The Completers population will be the analysis population for the primary objective hypothesis testing.

Missing Endpoint Data

Study centers will be instructed to make every effort to keep subjects actively attending study visits. The primary and secondary objective assessments are planned to be collected at the 3-Month follow-up

visit. If subjects miss their scheduled 3-Month follow-up visit, the investigator will attempt to collect the data within the visit window or before study discontinuation. Phone calls may also be utilized to obtain data for the primary endpoint.

Completers population: The Completers population will be analyzed without imputations for missing data. (By definition, the endpoint data was provided.) It is assumed that the primary reasons for missing endpoint data will be death or inability to contact subjects due to deteriorating health (Bagla[19]) and not related to pain score level. Thus, inclusion in the Completers population is assumed to not be confounded with endpoint pain score level.

Sensitivity Analysis: The Treated population is expected to have missing endpoint data. The frequency, timing, and reasons for missing data will be reported and analyzed to assess potential for bias. Sensitivity analyses of the primary objective, detailed in the primary objective analysis methods section below, will include analyzing the Treated population using multiple imputation and single imputation. The results of these analyses may suggest other specific sensitivity analyses or imputation strategies.

Adjustments for Multiple Endpoints

The primary objective will be tested at a two-sided alpha level of 0.05. There are no hypothesis tests associated with the secondary objective or additional measures, so no adjustment for multiple endpoints is required.

13.1.5. Interim analyses

There will be no formal interim statistical analyses.

13.1.6. Reports

Annual reports of study progress and safety data will be provided. The primary objective hypothesis will be tested and reported after the sample size requirements for it have been met, and a final study report will be prepared once final study data is collected.

13.2. Demographics

Demographic characteristics and baseline cancer and pain history will be summarized for all enrolled and treated subjects.

13.3. Primary Objective

13.3.1. Primary objective

To demonstrate an improvement from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in only the thoracic and/or lumbar vertebral body(ies)

13.3.2. Hypothesis

H_0: $\mu_c = 0$

H_A: $\mu_c \neq 0$

Where μ_c is the mean change from baseline to the 3-Month Visit in worst-pain score.

13.3.3. Data Collection

At the baseline and 3-Month study visits, the worst pain question in the BPI will be used to evaluate the pain severity:

> Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours (circle only one number, 0-10). No pain = 0, Pain as bad as you can imagine = 10

13.3.4. Endpoint Definition

Change in pain will be calculated as:

μ_c = worst-pain $_{3\text{-month}}$ – worst-pain $_{baseline}$

A negative value for change in pain represents a lowering of the subject's pain score (an improvement, or reduction in pain) and a positive value represents an increase in the subject's pain score (a worsening, or increase in pain).

13.3.5. Sample Size Methods and Assumptions

The standard deviation of change from Greenwood et al (2015)[40] is estimated to be 4.1 at 4 weeks. The standard deviation of change in the CAFE study Berenson et al (2011)[41] was 3.2 at 1 month. The standard deviation of change from Lane et al (2011)[42] is estimated to be 2.4 at 1 day post-procedure. It is not known which of those studies will most closely match the population and test conditions in this study. The median of those 3 studies is 3.2. To account for this study having a longer follow-up period and a more diverse patient population, and thus more opportunity for variability, the standard deviation for our sample size calculation will be increased to 3.5.

The minimal clinically important difference (MCID) of 2 points was used to interpret pain score differences in terms of clinical relevance in Bagla et al (2016)[19] and a clinically significant change in pain of 2 points was also identified in Greenwood[40]. This will be used for our calculations.

Bagla[19] followed subjects for 3 months post procedure. They reported that pain scores were provided for 68% of subjects (32% not provided) at 3 months. This will be used for our calculations.

The PASS program used to calculate the sample size was the one-sample t-test power analysis, $mean_0$=0, $mean_A$=2, standard deviation (of change) =3.5, two-sided significance level (alpha)=0.05, and power=0.90. The required sample size was 35. To account for subjects getting treated but not providing the 3-Month data, the treated sample size is adjusted for a 32% loss, to 52.

13.3.6. Analysis Methods

A two-sided t-test with alpha=0.05 will be used to test the null hypothesis of no change in worst-pain score between baseline and 3 months.

If the distribution of the change scores does not meet the assumption of normality, the non-parametric Wilcoxon signed-rank test will be used to test for significant change with alpha=0.05, two-sided.

The primary objective hypothesis will be tested after the sample size requirements for it have been met. If additional subjects are enrolled later and also treated for metastatic lesions involving only the vertebral body, those additional subjects will be combined with the first group and summarized together.

The main analysis for the primary objective hypothesis testing will be on the Completers population.

In order to include all the treated subjects in the analysis, a sensitivity analysis will be performed on the Treated population. The endpoint data will first undergo multiple imputations (MI). Rather than filling in a single value for each missing value, MI replaces each missing value with a set of "plausible" values that represent the uncertainty about the correct value to impute. These multiple imputed datasets are then analyzed using standard statistical procedures and then combined into one analysis result with an appropriately increased variance. Included in the MI analysis will be the endpoint variable at 3 months and the endpoint variable at baseline, 3 days, 1 week, 1 month, and unscheduled visits (if collected), as well as baseline covariates. The method to be used is the Markov chain Monte Carlo (MCMC) method of SAS (version 9.4 or higher). This is an iterative method that can be used when the pattern of missing data is arbitrary (monotone or non-monotone). The default number of iterations will be used (n=5) and, if needed, will be increased until the Markov chain converges.

A single imputation method will also be performed, substituting the Treated population's endpoint variable at the last available follow-up (Bagla[19]) for the missing endpoint variable.

Sensitivity analyses will be performed, separating the evaluation by whether or not the subjects received vertebral augmentation procedures and/or post RFA radiation therapy.

13.4. Secondary Objective

The data collection and endpoint definition for the secondary objective will be the same as for the primary objective.

13.4.1. Secondary objective

To characterize change from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in the periacetabulum, iliac crest, and/or sacrum, and for benign bone tumors

13.4.2. Hypothesis

There is no formal hypothesis. The objective is to characterize the change in pain.

13.4.3. Data Collection

At the baseline and 3-Month study visits, the worst pain question in the BPI will be used to evaluate the pain severity:

> Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours (circle only one number, 0-10). No pain = 0, Pain as bad as you can imagine = 10.

13.4.4. Endpoint Definition

Change in pain will be calculated as:

$$\mu_c = \text{worst-pain}_{\text{3-month}} - \text{worst-pain}_{\text{baseline}}$$

A negative value for change in pain represents a lowering of the subject's pain score (an improvement, or reduction in pain) and a positive value represents an increase in the subject's pain score (a worsening, or increase in pain).

13.4.5. Sample Size Methods and Assumptions

There are no sample size requirements or calculations for the secondary objective.

13.4.6. Analysis Methods

The Treated and Completers populations will both be reported on.

Descriptive statistics, as well as confidence intervals, of the change in pain will be reported.

The subsets of subjects in the secondary objective cohort (subjects with metastatic lesions outside the vertebral body and/or benign bone tumors) will be reported on as a whole, and also individually (metastatic lesions outside the vertebral body, benign bone tumors, and combinations which may also include metastatic lesions involving the vertebral body.)

13.5. Safety Measure

Characterize incidence of all device, procedure and/or therapy related adverse events and device deficiencies from enrollment to the 12-Month Visit.

13.5.1. Data Collection and Endpoint Definitions

Reported adverse events and device deficiencies will be collected on eCRFs. They will be coded and summarized using the Medical Dictionary for Regulatory Affairs (MedDRA). They will also be categorized by relationship to the device, procedure, or therapy.

Adverse events that occur concurrently to device deficiencies will be reported using the adverse event system.

13.5.2. Analysis Methods

The Enrolled subjects will be included in the safety measures. Analyses of deaths will be presented using the final CEC determination.

Device, therapy, and/or procedure related events will be presented separately from SAEs that are not related. Adverse events will be presented in summary tables displaying the number of serious events, the number of events, the number of subjects with ≥1 event, and the percentage of subjects with ≥1 event. The events will be presented by system organ class (SOC) and preferred term (PT). The events will also be presented sorted in descending order of frequency overall. Adverse event tables will be displayed by study phase where applicable. Adverse events may be reported using the classification system used by the Society of Interventional Radiology[43].

Device deficiencies will be presented in summary tables similar to adverse events.

13.6. Additional Measures

- [redacted]

Statistical results will be presented in the reports following the standard business unit clinical study report templates.

14. Ethics

14.1. Statement(s) of Compliance

The study will be conducted in accordance with this protocol and the ethical principles that have their origin in the Declaration of Helsinki.

In the US, the study will be conducted in accordance with 21 CFR§11 Electronic Records, Electronic Signatures, 21CFR§50 Protection of Human Subjects, 21 CFR§54 Financial Disclosure by Clinical Investigators, 21CFR§56 IRB, and 21CFR§803 Medical Device Reporting.

In Europe, the study will be conducted in accordance with 21 CFR§11 Electronic Records and Electronic Signatures, 21 CFR§54 Financial Disclosure by Clinical Investigators, and any regional or national regulations, as appropriate.

In Canada, the study will be conducted in accordance with Canada Medical Devices Regulations,1998 (SOR/98-282), and the Guidance document for Mandatory Problem Reporting for Medical Devices, 2011(H164-145/201E).

The principles of the Declaration of Helsinki have been implemented in this study by means of the patient informed consent process, IRB/EC approval, risk benefit assessment, study training, clinical trial registration, and publication policy. Study Investigators will be required to sign an Investigator Statement stating their intent to adhere to applicable regulations.

The clinical investigation shall not begin at any site until the required approval/favorable opinion from the Ethics Committee (EC)/Institutional Review Board (IRB) or notification/approval from a regulatory authority have been obtained, if appropriate.

Any additional requirements imposed by the EC/IRB or regulatory authority shall be followed, if appropriate.

14.2. Principal Investigator Obligation

The principal investigator will provide adequate oversight to ensure the study is conducted in accordance with all protocol requirements, all applicable regulatory requirements and any applicable institutional requirements related to the conduct of human clinical research. The principal investigator will ensure no study-related activities occur prior to regulatory and IRB/EC approval. Any actions taken by the IRB/EC with respect to the investigation will be forwarded to Medtronic as soon as possible.

The principal investigator is responsible for submitting all required reports to the sponsor and/or IRB/EC. Table 14-1 provides a summary of minimum investigator reporting responsibilities for the US, EUR, and CAN.

Regulatory reporting of AEs/DDs will be completed according to local regulatory requirements. It is the responsibility of the Investigator to abide by any additional AE/DD reporting requirements stipulated by the IRB/EC responsible for oversight of the study. Investigators should report device, procedure and therapy related adverse events and device deficiencies to Medtronic immediately after the Investigator learns of the event.

In addition, the principal investigator will provide Medtronic with the following minimum information related to device/therapy and/or procedure-related adverse events and device deficiencies:

- *Date of adverse event or device deficiency*
- *Treatment provided*
- *Resolution date*

- *Assessment of severity*
- *Assessment of seriousness*
- *Relationship to the device, therapy and/or procedure*

Failure to perform the investigator obligations or to complete corrective and preventive actions identified during monitoring or auditing activities may result in principal investigator or site personnel disqualification, and/or lead to suspension or termination of the study at the site.

14.3. Investigator Reporting Requirements – Europe

Table 14-1 includes minimum reporting requirements for investigators participating in studies in Europe. Medtronic study personnel will immediately report Adverse Events and Device Deficiencies, related to a CE marked device used during the study, to Medtronic's Complaint Handling Unit who will ensure prompt review, and appropriate reporting.

14.4. Reporting Requirements for Canada[44]

The Therapeutic Products Directorate is a division of Health Canada, and is responsible for regulating therapeutic products including Foods, Drugs, Medical Devices, Natural Health Products, Cells, Tissues and Organs, and Cosmetics. Table 14-1 includes minimum reporting requirements in Canada.

Table 14-1: Reporting Requirements for US, EUR and CAN

Serious Adverse Events(SAEs)	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event **All other geographies:** Report to the sponsor, without unjustified delay, all serious adverse events.
EC/IRB	**All geographies:** Reporting timeframe as per local EC/IRB per local requirement
Sponsor submit to:	
EC/IRB	**All geographies:** Reporting timeframe as per local EC/IRB per local requirement
Regulatory Authorities	**All geographies:** Reporting timeframe as per local requirement
Serious Adverse Device Effects (SADEs)	

Investigator submit to:	
Medtronic	**US:** • *Submit to Medtronic within 24 hours after the Investigator first learns of the SADE.* • *Submit to IRB/EC per local requirements.* **Europe:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event **All other geographies:** Submit as soon as possible after the Investigator first learns of the event, and per local requirements
EC/IRB	**US: Submit to IRB, if required:** • *Submit to Medtronic within 24 hours after the Investigator first learns of the SADE.* • *Submit to IRB/EC per local requirements.* **All other geographies:** Reporting timeframe as per local EC/IRB requirement
Sponsor submit to:	
EC/IRB	**All geographies:** Reporting timeframe as per local EC/IRB per local requirement
Regulatory Authorities	**Canada (Medtronic of Canada Regulatory Compliance) to submit to Health Canada:** As **soon** as possible to meet regulatory reporting requirements within **10 days** after the date Medtronic becomes aware. **All other geographies:** Reporting timeframe as per local requirement
Unanticipated Serious Adverse Device Effects (USADEs) and Unanticipated Adverse Device Effects (UADEs)	
Investigator submit to:	
Medtronic	**US:** Submit to Medtronic and IRB within **10** working days after the Investigator first learns of the effect. **Europe:** Immediately after the investigator first learns of the event or of new information in relation with an already reported event

	All other geographies: Submit as soon as possible after the Investigator first learns of the event, and per local requirements
EC/IRB	**US:** Submit to Medtronic and IRB within **10** working days after the Investigator first learns of the effect. **All other geographies**: Reporting timeframe as per local EC/IRB requirement
Sponsor submit to:	
Investigators	**All geographies:** Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect.
EC/IRB	**US** Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect. **All Other geographies:** Reporting timeframe as per local requirement
Regulatory Authorities	**US:** Notification as soon as possible to the Food and Drug Administration (FDA), but not later than 10 working days after the sponsor first learns of the effect. **Europe:** Reporting timeframe as per local requirement **Canada (Medtronic of Canada Regulatory Compliance) to submit to Health Canada:** As soon as possible to meet regulatory reporting requirements within **10 days** after the date Medtronic becomes aware.
All Other Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the event.
EC/IRB	**All geographies:** Reporting timeframe as per local EC/IRB requirement
Deaths	
Investigator submit to:	

Medtronic	**All geographies:** All subject deaths must be reported to Medtronic and the IRB/EC as soon as possible, but **no more than 5 working days** of learning of a subject's death, regardless of whether or not the death is related to the device system or therapy.
EC/IRB	**All geographies:** All subject deaths must be reported to Medtronic and the IRB/EC as soon as possible, but **no more than 5 working days** of learning of a subject's death, regardless of whether or not the death is related to the device system or therapy.
USADE, SADE, DD (Canada only) (referred to here as "incidents") occurring outside Canada requiring corrective action or imposed by local regulatory authorities)	
Sponsor submit to:	
Regulatory Authorities	**Canada (Medtronic of Canada Regulatory Compliance):** When Medtronic has indicated to a regulatory authority of the country in which the incident occurred, intention to take corrective action, or if the regulatory authority has required Medtronic to take corrective action. In this case, the incident must be reported to the Health Canada as soon as possible after either Medtronic has reported to the local regulatory authority or a corrective action has been imposed by the local regulatory authority.
Device Deficiencies that has resulted in an SAE (Canada only)	
Sponsor submit to:	
Regulatory Authorities	**Canada (Medtronic of Canada Regulatory Compliance) to submit report to Health Canada:** As soon as possible to meet regulatory reporting requirements within **10 days** after the date Medtronic becomes aware.
Device Deficiencies (DD) with SADE potentials	
Investigator submit to:	
Medtronic (and to EC/IRB if required)	**US:** • *Submit to Medtronic Device Deficiencies that could have led to a SADE within **24 hours** after the Investigator first learns of the Device Deficiency.*

	• *Submit Device Deficiencies that could have led to a SADE to IRB/EC, per local requirements.* **Europe:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency **All geographies:** Report to the sponsor, without unjustified delay, all device deficiencies that could have led to a serious adverse device effect
EC/IRB	**US: Submit to IRB, if required:** • *Submit to Medtronic Device Deficiencies that could have led to a SADE within **24 hours** after the Investigator first learns of the Device Deficiency.* • *Submit Device Deficiencies that could have led to a SADE to IRB/EC, per local requirements.* **All other geographies:** Reporting timeframe as per local EC requirement
Sponsor submit to:	
EC/IRB	**All geographies:** Reporting timeframe as per local EC requirement
Regulatory Authorities	**Canada (Medtronic of Canada Regulatory Compliance) submits to Health Canada:** As soon as possible to meet regulatory reporting requirements within **30 days** after the date Medtronic becomes aware. **All other geographies:** Reporting timeframe as per local requirement
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the deficiency
EC/IRB	**All geographies:** Reporting timeframe as per local EC requirement
Withdrawal of IRB Approval	
Investigator submit to:	
Medtronic	**All geographies:** Report a withdrawal of the reviewing EC/IRB approval within **5 days** of investigator notification.

Progress Report	
Investigator submit to:	
Medtronic	**US**: The Investigator must submit a progress report on an annual basis if the study lasts longer than one year.
EC/IRB	**US**: The Investigator must submit a progress report on an annual basis if the study lasts longer than one year.
Protocol Deviations for Emergency Reasons	
Investigator submit to:	
Medtronic	**US:** Submit to Medtronic and IRB **within 5 working** days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). **Canada:** Per institutional guidelines, report protocol deviations to the reviewing IRB.
EC/IRB	**US:** Submit to Medtronic and IRB **within 5 working** days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). **Canada:** Per institutional guidelines, report protocol deviations to the reviewing IRB.
Prior Notification of Protocol Deviations	
Investigator submit to:	
Medtronic	**All geographies:** Except in the occurrence of an emergency deviation, the Investigator must obtain prior approval from Medtronic of protocol deviations. Prior approval from the IRB may also be required according to local requirements.
EC/IRB	**All geographies:** Except in the occurrence of an emergency deviation, the Investigator must obtain prior approval from Medtronic of protocol deviations. Prior

	approval from the IRB may also be required according to local requirements.
Failure to Obtain Informed Consent	
Investigator submit to:	
Medtronic	**US and Europe:** The Investigator must notify Medtronic within **5 working days** upon awareness **Canada:** The Investigator must notify Medtronic within **5 working** days after procedure.
EC/IRB	**US and Europe:** The Investigator must notify Medtronic within **5 working days** after upon awareness **Canada:** The Investigator must notify Medtronic within **5 working** days after procedure.
Final Report	
Investigator submit to:	
Medtronic	**US and Europe:** Study reports must be submitted within **6 months** after termination or completion of the investigation or as required by applicable regulation. **Canada:** Study reports must be submitted within **3 months** after termination or completion of the investigation or as required by applicable regulation.
EC/IRB	**US and Europe:** Study reports must be submitted within **6 months** after termination or completion of the investigation or as required by applicable regulation. **Canada:** Study reports must be submitted within **3 months** after termination or completion of the investigation or as required by applicable regulation.

14.5. Oversight of Study Personnel

The principal investigator will delegate study-related tasks to appropriate trained and qualified personnel to ensure alignment between contractual obligations and delegated study responsibilities.

The delegation of study-related tasks will be documented and the principal investigator will provide ongoing oversight of all delegated study-related tasks.

The principal investigator will ensure good clinical practice and protocol specific training is provided, completed and documented for all staff performing delegated study-specific tasks.

Study center personnel participating in the clinical study will be trained in study activities relevant to their role. Training must be completed and documented prior to that individual conducting any study-related activities.

Investigator and/or study coordinator meeting(s) or telephone conference call(s) may be held to discuss the Clinical Investigation Plan (CIP), training, study results, etc. Continued training may occur through interim meetings or telephone conference calls to discuss relevant study issues.

14.6. Medtronic Representative Role

Medtronic representatives who are qualified and trained on the protocol and applicable study regulations may support study conduct under the direct supervision of the principal investigator as described below. The principal investigator or a clinical person designated on the delegation of authority form must be present to collect source documentation, record the study activities, and to be responsive to the subject's needs during an activity performed by a Medtronic representative.

Medtronic personnel may:

- *Provide technical support during the procedure and follow-up visits*
- *This support may include the training of site personnel on the use of the Medtronic equipment or CIP-related procedures and data collection*
- *Clarify device behavior, operation, or diagnostic output as requested by the Principal Investigator or other health care professional*
- *Assist with the collection of study data during the procedure (technical worksheets)*

Medtronic personnel may not:

- *Practice medicine, provide medical diagnoses or make decisions related to subject treatment/care*
- *Express opinions about the product/feature under study*
- *Assist the subject by direct physical contact except as required by the specific protocol-related task to be conducted*
- *Discuss a subject's condition or medical treatment with the subject or a member of the subjects family*
- *Provide the subject with any form/questionnaires related to the product(s) under investigation*
- *Enter data on eCRFs, except on the Medtronic Use Only Field*

15. Study Administration

15.1. Monitoring

Medtronic is responsible for ensuring the proper conduct of this study in terms of adherence to applicable regulations, protocol compliance, and the validity and accuracy of the study data entered on eCRFs.

Monitoring and monitoring oversight will be provided by Medtronic personnel or by representatives of Medtronic (i.e. contractors and other designees) who will support the study investigation including site qualification, site initiation, interim monitoring and study closure visits.

Contact information for the study monitoring:

Medtronic Core Clinical Solutions
8200 Coral Sea Street, N.E., MVS33

Mounds View, MN 55112, USA

The Principal Investigator and site personnel will provide the Medtronic monitor(s) with complete access to primary source data (e.g., paper and electronic hospital/clinical charts, appointment books, laboratory records) that support the data on the eCRFs as well as other documentation supporting the conduct of the study. The monitor will perform source data verification and routine reviews of study-related regulatory documents during scheduled monitoring visits and work to secure compliance should any deficiencies be observed. Monitoring frequency may be increased if there are changes in study center personnel (to allow for training and additional sponsor oversight), a protocol amendment/safety issue that significantly affects study procedures or design, a documented or suspected lack of study compliance or investigator oversight, or an issue with recruitment or enrollment.

15.2. Data Management

Medtronic personnel will perform routine edit and consistency checks for items such as missing data or inconsistent data. Identified data inconsistencies will be resolved by use of data discrepancies; investigators and site personnel will review data discrepancies and respond to the discrepancies in a timely manner. The resolved discrepancy will become a part of the eCRF record for the subject.

The Oracle Clinical Remote Data Capture (RDC) system which is 21CFR§11 Part E compliant controls user access and ensures data integrity. This system is a fully validated system. The RDC system maintains an audit trail of entries, changes or corrections in eCRFs. User access will be granted to each individual based on his or her delegation of authority and completion of required training. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the system will require the Principal Investigator, or authorized delegate, to re-sign the eCRF.

The Principal Investigator, or designated representative, is responsible for the data submitted and must review all data for accuracy and provide his/her approval of the eCRF and sign each form with an electronic signature.

Data directly retrieved from the OsteoCool RF Ablation generator after the completion of the procedure should be transmitted to Medtronic over a secure server.

15.3. Direct Access to Source Data/Documents

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

Medtronic or third-party auditors representing Medtronic may perform Quality Assurance audits to verify the performance of the monitoring process and study conduct, and to ensure compliance with applicable regulations. Representatives for regulatory bodies such as the FDA may also perform site inspections related to this clinical study. The Principal Investigator, site personnel, and institution will provide auditors with direct access to primary source data and all study-related documentation.

Medtronic will investigate and report suspected cases of fraud or misconduct as appropriate.

15.4. Confidentiality

Subject confidentiality is assured through the use of subject identification numbers and the de-identifying of images and medical records obtained by the Sponsor. In addition to the review of records on site, release of de-identified records to Medtronic may be necessary, such as in the evaluation of adverse events.

For purposes of monitoring this study, access to clinic and hospital records must be available to Medtronic, agents of Medtronic (e.g. CRO), the FDA, and other regulatory agencies.

(US only) Health Insurance Portability and Accountability Act (HIPAA) language will be required to be included at every site. HIPAA language may be included within the ICF template.

15.5. Liability

Medtronic is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC, the governing regulatory authority (if applicable), and/or the IRB.

15.6. CIP Amendments

Protocol amendments may be initiated by Medtronic to address changes to the conduct of the study. Protocol amendments must be approved by Medtronic and submitted to the IRB/ECs and/or the governing regulatory authority (if applicable); protocol amendment approval and approval of any associated changes to the informed consent document must be obtained prior to implementation of the amendment except:

- When necessary to eliminate an immediate/or apparent immediate hazard to participating subjects

- When the change involves purely administrative or logistical aspects of the study

15.7. Record Retention

At a minimum the investigator is responsible for the preparation, review, and retention of the records listed below:

- Essential correspondence that pertains to the investigation
- Records of each subject's case history and exposure to the procedure/therapy
- Case histories include the eCRFs and supporting data (source documentation), such as:
    - Signed and dated ICFs
    - Medical records, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurse's notes
    - Subject assessments/questionnaires
    - All reportable adverse event information
    - Data related to the OsteoCool procedure
- Documentation of any deviation to the protocol, including the date and the rationale for such deviation
- Signed Investigator Agreement and curriculum vitae for all Investigators
- Delegation of Authority
- Training records
- The protocol and any amendments

The Principal Investigator is responsible for ensuring that all essential study documentation is retained and accessible for a minimum of 2 years following completion of the study or based on the country specific requirement, the longest retention data applies. The Principal Investigator will ensure that essential study documents are not destroyed until written permission has been obtained from Medtronic. Medtronic will be notified in writing of any transfer of study documentation.

15.8. Publication and Use of Information

Medtronic intends to publish the results from the OsteoCool study in a timely manner as data become available. These publication activities may include abstracts, presentations/posters to scientific meetings, and manuscripts.

Investigators who gathered data for this study (i.e., enrolled subjects and complied with the protocol) may be asked to write or contribute to the writing of abstracts and manuscripts based on the results of this study. Principal investigators who meet the study-specific criteria above will be considered for abstract/manuscript authorship if they meet the International Committee of Medical Journal Editors, Ethical Considerations in the Conduct and Reporting of Research criteria available via the following link: http://www.icmje.org. Specifically, authorship credit should be based on the following and should meet all criteria listed below:

- Substantial contributions to conception or design; or the acquisition, analysis and interpretation of data for the work;

- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Medtronic employees who meet the International Committee of Medical Journal Editors criteria for authorship will have the right to authorship.

All contributors who do not meet the criteria for authorship are to be listed in an acknowledgments section according to the guidelines of the applicable scientific journal. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair that provided only general support.

Before publication of any study-related data, the following guidelines will apply:

- *Investigators are obligated to provide Medtronic with an opportunity to review any publication developed from data derived from this study.*
- *Medtronic will not financially compensate health care professionals (HCPs) or health care organizations (HCOs) for writing or editing activities on scientific publications related to research sponsored by Medtronic.*

15.9. Suspension or Early Termination

Medtronic reserves the right to suspend or terminate the study at any time. Reasons may include, but are not limited to, the following:

- *Insufficient enrollment to complete the study within the expected timeframe*
- *Identification of unacceptable safety profile; suspicion of an unacceptable risk will result in a suspension, confirmation of an unacceptable risk will result in termination*
- *Product performance/product supply issues*
- *EC/IRB/the governing regulatory authority (if applicable) suspension and/or termination of the study*

Medtronic reserves the right to suspend or terminate the study at an individual site. Reasons may include, but are not limited to, the following:

- *Noncompliance with the protocol*
- *Serious or repeated deviations at the site*
- *Failure to implement required corrective and preventive actions*
- *Insufficient enrollment to complete the study within the expected timeframe*
- *Loss of appropriately trained site personnel*

Investigators are required to notify the IRB/EC of study suspension/termination. Subjects will be notified by the investigator of suspension/termination due to unacceptable risk or of termination due to any other cause.

If, for any reason, Medtronic suspends or prematurely terminates the investigation at an individual investigation site, Medtronic shall inform the responsible regulatory authority as appropriate and ensure

that the IRB/EC is notified, either by the Principal Investigator or by Medtronic. If the suspension or premature termination was in the interest of safety, Medtronic shall inform all other Principal Investigators and investigational sites. The Principal Investigator or authorized designee shall promptly inform the enrolled subjects at his/her investigation site, if appropriate.

16. References

1. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer*. 2002;2(8):584-593. doi:10.1038/nrc867.
2. Su Y, Sun Z-Z, Shen L-X, et al. Comparison of percutaneous vertebroplasty with and without interventional tumor removal for spinal metastatic tumor without epidural involvement. *J Bone Oncol*. 2017;6:1-7. doi:10.1016/j.jbo.2016.12.002.
3. Pellerin O, Medioni J, Vulser C, Dean C, Oudard S, Sapoval M. Management of painful pelvic bone metastasis of renal cell carcinoma using embolization, radio-frequency ablation, and cementoplasty: a prospective evaluation of efficacy and safety. *Cardiovasc Intervent Radiol*. 2014;37(3):730-736. doi:10.1007/s00270-013-0740-x.
4. Fairchild A. Palliative radiotherapy for bone metastases from lung cancer: Evidence-based medicine? *World J Clin Oncol*. 2014;5(5):845-857. doi:10.5306/wjco.v5.i5.845.
5. Hoffmann RT, Jakobs TF, Trumm C, Weber C, Helmberger TK, Reiser MF. Radiofrequency ablation in combination with osteoplasty in the treatment of painful metastatic bone disease. *J Vasc Interv Radiol*. 2008;19(3):419-425. doi:10.1016/j.jvir.2007.09.016.
6. Jacofsky DJ, Papagelopoulos PJ, Sim FH. Advances and challenges in the surgical treatment of metastatic bone disease. *Clin Orthop Relat Res*. 2003;(415 Suppl):S14-S18. doi:10.1097/01.blo.0000093046.96273.07.
7. Agarawal JP, Swangsilpa T, van der Linden Y, Rades D, Jeremic B, Hoskin PJ. The role of external beam radiotherapy in the management of bone metastases. *Clin Oncol (R Coll Radiol)*. 2006;18(10):747-760. https://libcontent.medtronic.com:2908/pubmed/17168210.
8. Johnstone C, Lutz ST. External beam radiotherapy and bone metastases. *Ann Palliat Med*. 2014;3(2):114-122. doi:10.3978/j.issn.2224-5820.2014.04.06.
9. Goetz MP, Callstrom MR, Charboneau JW, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol*. 2004;22(2):300-306. doi:10.1200/JCO.2004.03.097.
10. Wallace AN, Robinson CG, Meyer J, et al. The Metastatic Spine Disease Multidisciplinary Working Group Algorithms. *Oncologist*. 2015;20(10):1205-1215. doi:10.1634/theoncologist.2015-0085.
11. Dupuy DE, Liu D, Hartfeil D, et al. Percutaneous radiofrequency ablation of painful osseous metastases: a multicenter American College of Radiology Imaging Network trial. *Cancer*. 2010;116(4):989-997. doi:10.1002/cncr.24837.
12. Guenette JP, Lopez MJ, Kim E, Dupuy DE. Solitary painful osseous metastases: correlation of imaging features with pain palliation after radiofrequency ablation--a multicenter american college of radiology imaging network study. *Radiology*. 2013;268(3):907-915. doi:10.1148/radiol.13122398.

13. Zheng L, Chen Z, Sun M, et al. A preliminary study of the safety and efficacy of radiofrequency ablation with percutaneous kyphoplasty for thoracolumbar vertebral metastatic tumor treatment. *Med Sci Monit*. 2014;20:556-563. doi:10.12659/MSM.889742.
14. Anchala PR, Irving WD, Hillen TJ, et al. Treatment of metastatic spinal lesions with a navigational bipolar radiofrequency ablation device: a multicenter retrospective study. *Pain Physician*. 2014;17(4):317-327. https://libcontent.medtronic.com:2908/pubmed/25054391.
15. Carrafiello G, Lagana D, Pellegrino C, et al. Percutaneous imaging-guided ablation therapies in the treatment of symptomatic bone metastases: preliminary experience. *Radiol Med*. 2009;114(4):608-625. doi:10.1007/s11547-009-0395-5.
16. Callstrom MR, Charboneau JW, Goetz MP, et al. Image-guided ablation of painful metastatic bone tumors: a new and effective approach to a difficult problem. *Skeletal Radiol*. 2006;35(1):1-15. doi:10.1007/s00256-005-0003-2.
17. Pezeshki PS, Akens MK, Gofeld M, Woo J, Whyne CM, Yee AJM. Bone targeted bipolar cooled radiofrequency ablation in a VX-2 rabbit femoral carcinoma model. *Clin Exp Metastasis*. 2015;32(3):279-288. doi:10.1007/s10585-015-9703-8.
18. Pezeshki PS, Woo J, Akens MK, et al. Evaluation of a bipolar-cooled radiofrequency device for ablation of bone metastases: preclinical assessment in porcine vertebrae. *Spine J*. 2014;14(2):361-370. doi:10.1016/j.spinee.2013.08.041.
19. Bagla S, Sayed D, Smirniotopoulos J, et al. Multicenter Prospective Clinical Series Evaluating Radiofrequency Ablation in the Treatment of Painful Spine Metastases. *Cardiovasc Intervent Radiol*. 2016;39(9):1289-1297. doi:10.1007/s00270-016-1400-8.
20. David E, Kaduri S, Yee A, et al. Initial single center experience: radiofrequency ablation assisted vertebroplasty and osteoplasty using a bipolar device in the palliation of bone metastases. *Ann Palliat Med*. January 2017. doi:10.21037/apm.2016.12.02.
21. Dierselhuis EF, van den Eerden PJM, Hoekstra HJ, Bulstra SK, Suurmeijer AJH, Jutte PC. Radiofrequency ablation in the treatment of cartilaginous lesions in the long bones: results of a pilot study. *Bone Joint J*. 2014;96-B(11):1540-1545. doi:10.1302/0301-620X.96B11.33544.
22. Zheng L, Chen Z, Sun M, et al. A preliminary study of the safety and efficacy of radiofrequency ablation with percutaneous kyphoplasty for thoracolumbar vertebral metastatic tumor treatment. *Med Sci Monit*. 2014;20:556-563. doi:10.12659/MSM.889742.
23. Deschamps F, Farouil G, de Baere T. Percutaneous ablation of bone tumors. *Diagn Interv Imaging*. 2014;95(7-8):659-663. doi:10.1016/j.diii.2014.04.004.
24. Anchala PR, Irving WD, Hillen TJ, et al. Treatment of metastatic spinal lesions with a navigational bipolar radiofrequency ablation device: a multicenter retrospective study. *Pain Physician*. 2014;17(4):317-327. https://libcontent.medtronic.com:2908/pubmed/25054391.
25. Gazis AN, Beuing O, Franke J, Jollenbeck B, Skalej M. Bipolar radiofrequency ablation of spinal tumors: predictability, safety and outcome. *Spine J*. 2014;14(4):604-608. doi:10.1016/j.spinee.2013.06.081.
26. Hillen TJ, Anchala P, Friedman MV, Jennings JW. Treatment of metastatic posterior vertebral body osseous tumors by using a targeted bipolar radiofrequency ablation device: technical note. *Radiology*. 2014;273(1):261-267. doi:10.1148/radiol.14131664.

27. Wallace AN, Huang AJ, Vaswani D, Chang RO, Jennings JW. Combination acetabular radiofrequency ablation and cementoplasty using a navigational radiofrequency ablation device and ultrahigh viscosity cement: technical note. *Skeletal Radiol*. 2016;45(3):401-405. doi:10.1007/s00256-015-2263-9.
28. Wallace AN, Tomasian A, Chang RO, Jennings JW. Treatment of Osteoid Osteomas Using a Navigational Bipolar Radiofrequency Ablation System. *Cardiovasc Intervent Radiol*. 2016;39(5):768-772. doi:10.1007/s00270-015-1243-8.
29. OsteoCool™ RF Ablation Probe Kit M708348B507E Rev. D.
30. Mathias SD, Crosby RD, Qian Y, Jiang Q, Dansey R, Chung K. Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form. *J Support Oncol*. 2011;9(2):72-78. https://libcontent.medtronic.com:2908/pubmed/21542414.
31. Callstrom MR, York JD, Gaba RC, et al. Research reporting standards for image-guided ablation of bone and soft tissue tumors. *J Vasc Interv Radiol*. 2009;20(12):1527-1540. doi:10.1016/j.jvir.2009.08.009.
32. Crooks V, Waller S, Smith T, Hahn TJ. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. *J Gerontol*. 1991;46(4):M139-M144. https://libcontent.medtronic.com:2908/pubmed/2071835.
33. Chow E, Hoskin P, Mitera G, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1730-1737. doi:10.1016/j.ijrobp.2011.02.008.
34. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208. https://libcontent.medtronic.com:2908/pubmed/10109801.
35. Groenvold M, Petersen MA, Aaronson NK, et al. EORTC QLQ-C15-PAL: the new standard in the assessment of health-related quality of life in advanced cancer? *Palliat Med*. 2006;20(2):59-61. https://libcontent.medtronic.com:2908/pubmed/16613400.
36. M708348B512_OsteoCool RF Ablation Probe Kit_revB.pdf.
37. OsteoCool™ Bone Access Kit M708348B462E Rev. B.
38. Pezeshki PS, Davidson S, Murphy K, et al. Comparison of the effect of two different bone-targeted radiofrequency ablation (RFA) systems alone and in combination with percutaneous vertebroplasty (PVP) on the biomechanical stability of the metastatic spine. *Eur Spine J*. 2016;25(12):3990-3996. doi:10.1007/s00586-015-4057-0.
39. Callstrom MR, Charboneau JW, Goetz MP, et al. Painful metastases involving bone: feasibility of percutaneous CT- and US-guided radio-frequency ablation. *Radiology*. 2002;224(1):87-97. doi:10.1148/radiol.2241011613.
40. Greenwood TJ, Wallace A, Friedman MV, Hillen TJ, Robinson CG, Jennings JW. Combined Ablation and Radiation Therapy of Spinal Metastases: A Novel Multimodality Treatment Approach. *Pain Physician*. 2015;18(6):573-581. https://libcontent.medtronic.com:2908/pubmed/26606009.
41. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncol*. 2011;12(3):225-235. doi:10.1016/S1470-2045(11)70008-0.

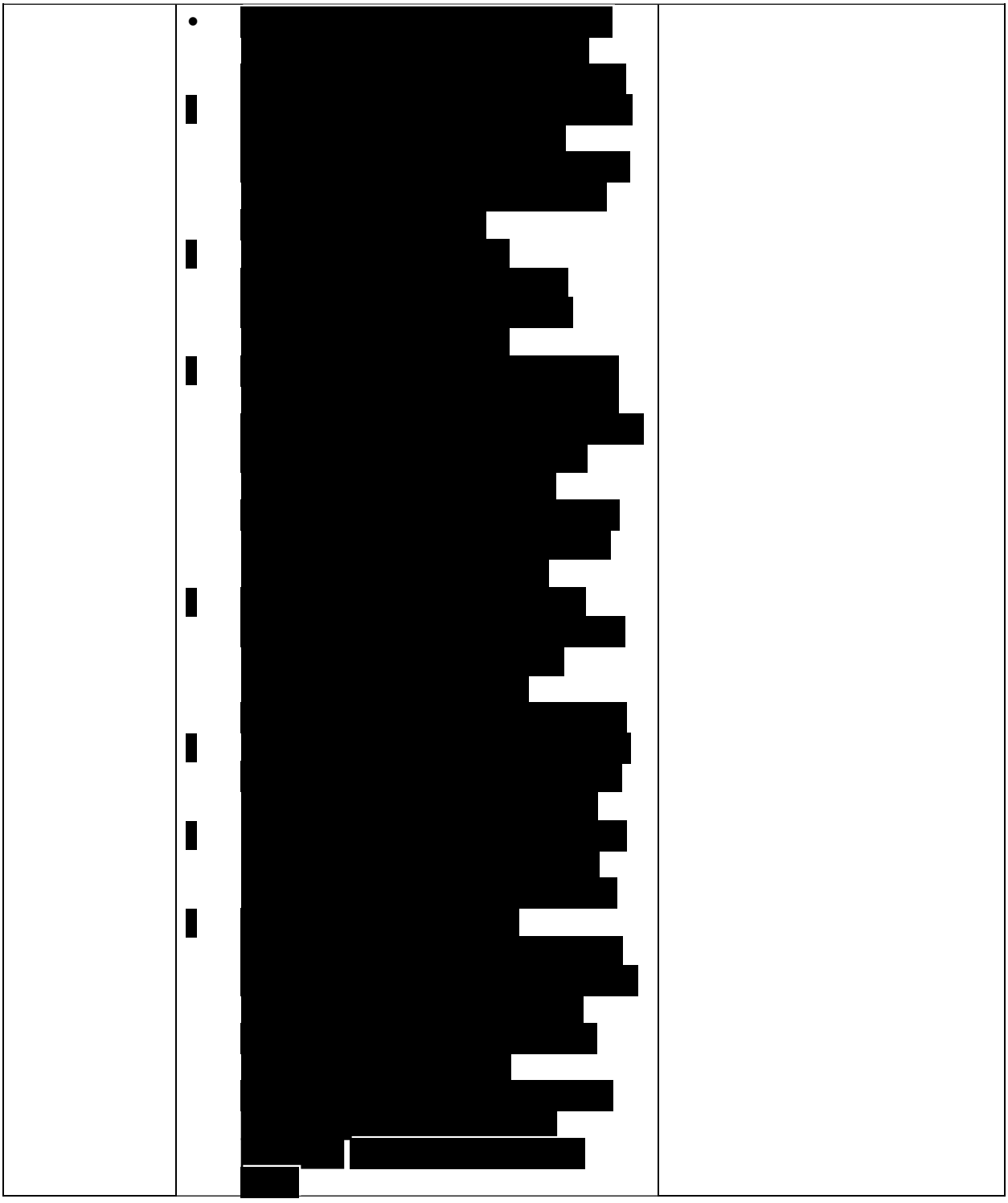
42. Lane MD, Le Huy BQ, Lee S, et al. Combination radiofrequency ablation and cementoplasty for palliative treatment of painful neoplastic bone metastasis: experience with 53 treated lesions in 36 patients. *Skeletal Radiol*. 2011;40(1):25-32. doi:10.1007/s00256-010-1010-5.
43. Callstrom MR, York JD, Gaba RC, et al. Research reporting standards for image-guided ablation of bone and soft tissue tumors. *J Vasc Interv Radiol*. 2009;20(12):1527-1540. doi:10.1016/j.jvir.2009.08.009.
44. Medtronic Global Safety Reporting Requirements for Clinical Studies 056-G140 version 5.0.

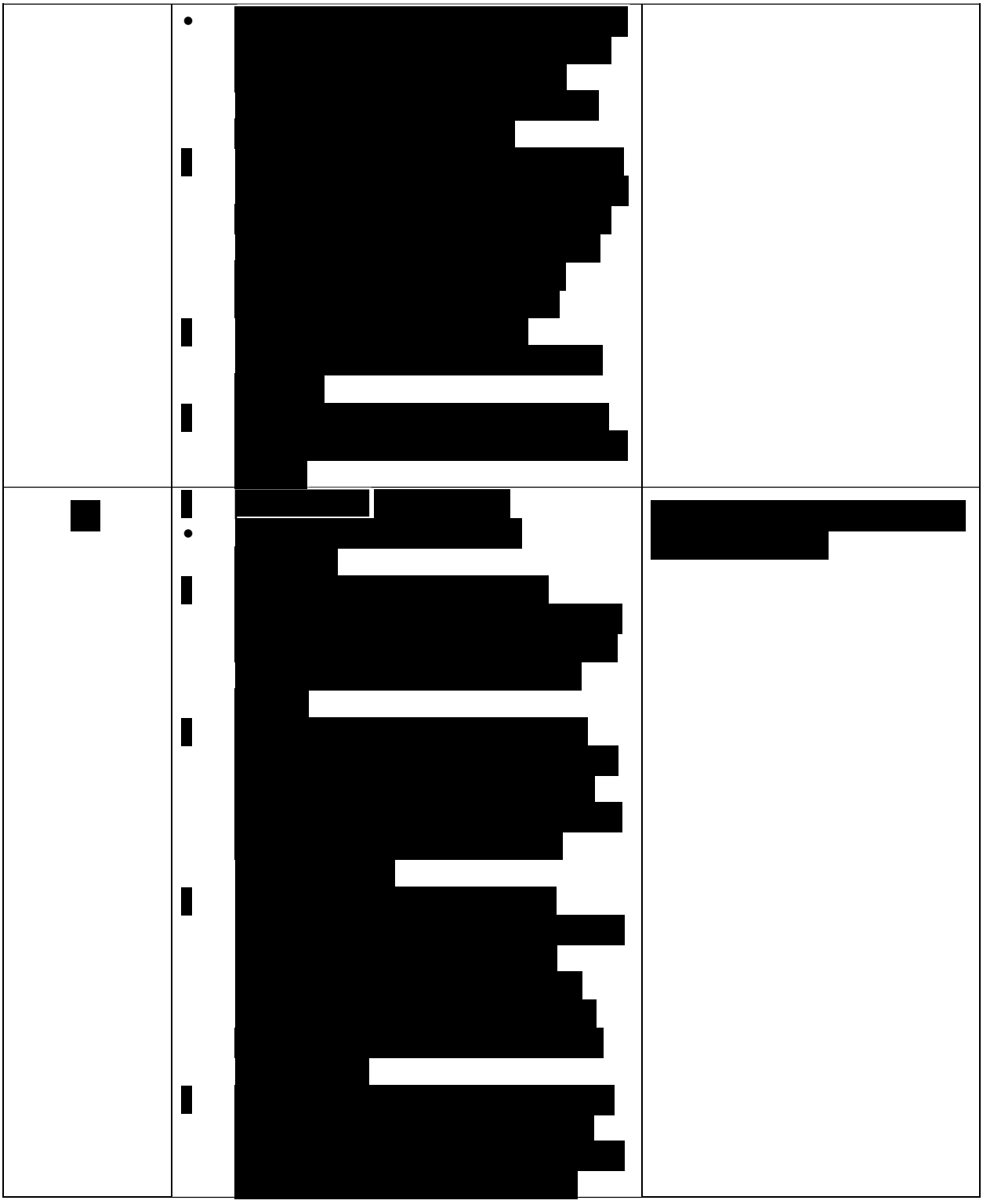
17. Appendices

Not applicable

18. Version History

Version	Summary of Changes	Author(s)/Title
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]





	[redacted]	
[redacted]	[redacted] *nd warning to align with updated labeling*	[redacted]

	• [redacted]	

Official Title of the study:	OsteoCool Tumor Ablation Post-Market Study (OPuS One)
NCT Number:	NCT03249584
Date of Document:	14 March 2019
Document Type:	Statistical Analysis Plan

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	OsteoCool Tumor Ablation Post-Market Study (OPuS One)
Clinical Investigation Plan Identifier	MDT16075
Clinical Investigation Plan Version	4.0
Sponsor/Local Sponsor	United States (Sponsor) Medtronic, Inc. 7000 Central Ave NE Minneapolis, MN, 55432 USA Europe (Local Sponsor): Medtronic International Trading Sàrl Route du Molliau 31 CH-1131 Tolochenaz, Switzerland Canada (Local Sponsor) Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada
Document Version	1.0

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
[redacted]	[redacted]	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
BPI	Brief Pain Inventory
CIP	Clinical Investigation Plan ('Protocol')
DD	Device Deficiency
MedDRA	Medical Dictionary for Regulatory Affairs
PT	Preferred Term
RF	Radiofrequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class

3. Introduction

The OsteoCool™ RF Ablation system is indicated in the United States (US), Europe (EUR) and Canada (CAN) for patients with metastatic malignant lesions in a vertebral body, painful metastatic lesions involving bone (in the US, patients with metastatic lesions involving the bone must have failed or were not candidates for standard therapy) and benign bone tumors such as osteoid osteomas.

The purpose of this prospective, multi-center, non-randomized, single arm study is to evaluate the effectiveness of the Medtronic OsteoCool™ RF Ablation system.

The scope of this Statistical Analysis Plan (SAP) includes the Primary Objective Report and the Final Study Report. The primary objective hypothesis will be tested and reported after the sample size requirements for it have been met, and a final study report will be prepared after final study data is collected.

4. Study Objectives

4.1 Primary Objective(s)

To demonstrate an improvement from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in only the thoracic and/or lumbar vertebral body(ies).

Worst pain score at the target treatment site will be collected from the Brief Pain Inventory (BPI).

4.2 Secondary Objective(s)

To characterize change from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in the periacetabulum, iliac crest, and/or sacrum, and for benign bone tumors.

Worst pain score at the target treatment site will be collected from the BPI.

4.3 Additional Measures

- [redacted]

4.4 Safety Measure

To characterize incidence of all device, procedure and/or therapy related adverse events and device deficiencies from enrollment to the 12-Month Visit.

5. Investigation Plan

This is a prospective, multi-center, non-randomized, post-market, single arm study designed to provide effectiveness outcomes on the Medtronic OsteoCool™ RF Ablation system.

The start of the study for each subject is defined as the date the subject first signs the informed consent. Enrolled subjects who do not meet baseline eligibility or who do not undergo the OsteoCool procedure will be exited from the study (e.g. RF therapy was not delivered). The completion of the study for each subject is defined as the conclusion of the 12 Month Visit (Study Exit). Each subject's participation in the study is expected to last approximately 1 year from the date of the OsteoCool procedure. Each subject will be evaluated prior to the OsteoCool procedure, during the procedure, prior to hospital discharge, 3 days, 1 week, 1-, 3-, 6-, and 12-months post procedure.

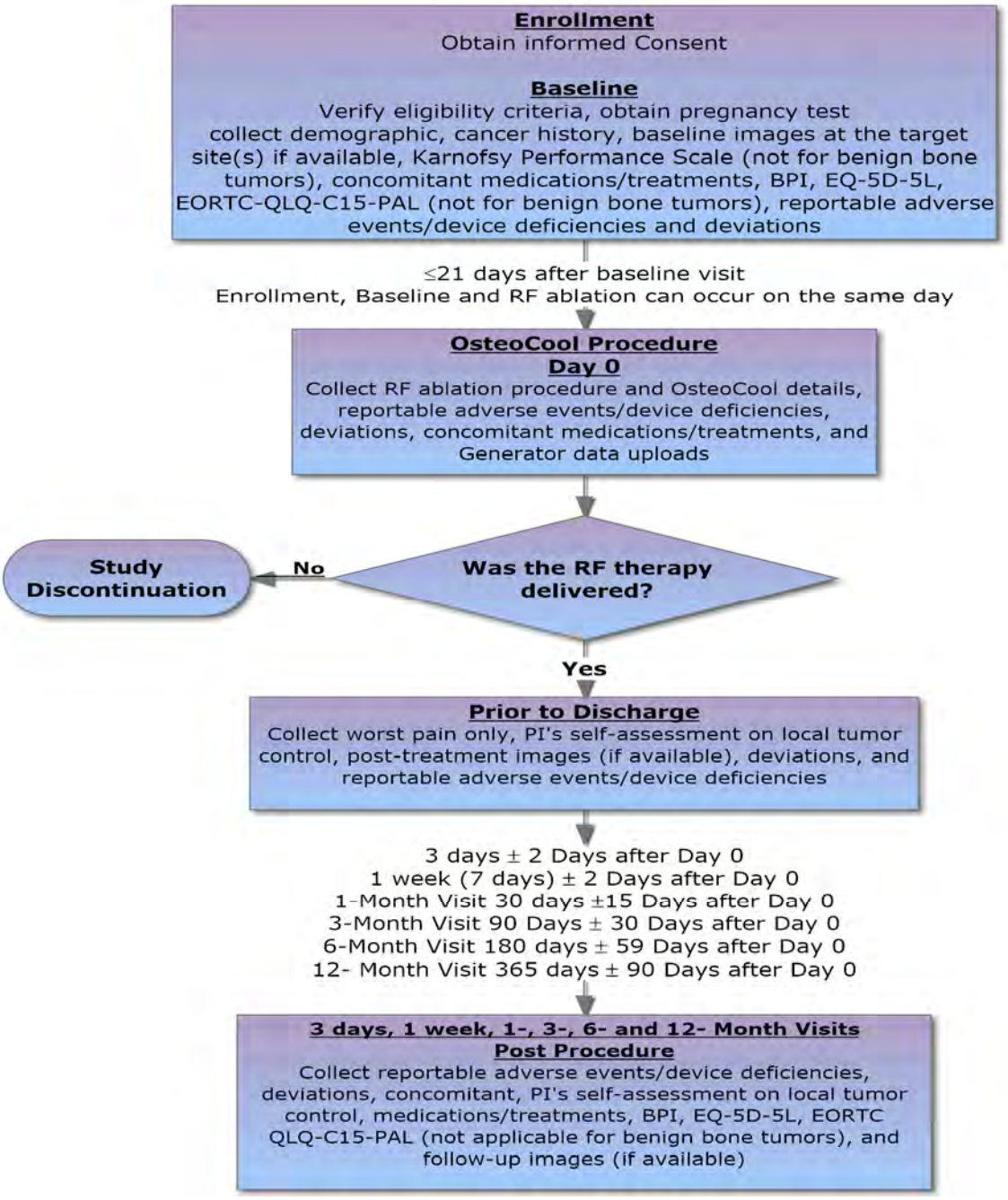
There is no randomization in the study.

After the sample size requirements for the primary objective hypothesis have been met, there will be a snapshot, and a *Primary Objective Report* will be prepared. The report will include testing of the primary objective hypothesis and only brief summaries of study subjects, non-primary objective efficacy and safety. The study will continue enrolling and following subjects after the report.

At the conclusion of the study, the data will be locked, and a *Final Study Report* will be prepared, which will include all evaluations (other than the primary objective). Additional subjects enrolled and treated for metastatic lesions involving only the vertebral body, that were not included in the Primary Objective Report will be combined with the subjects in the Primary Objective Report and summarized together in the Final Study Report. The primary objective will not be re-tested in this report. However, the results of the original primary objective hypothesis testing will be included for completeness.

Figure 5-1 outlines the study design and required follow-up requirements.

Figure 5-1: Study Design



6. Determination of Sample Size

Primary Objective Sample Size

The sample size calculations were performed using PASS 11 statistical software. (PASS 11 v. 11.0.7, Hintze J).

The primary objective is to demonstrate an improvement from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions involving only the vertebral body.

The standard deviation of change from Greenwood et al (2015) is estimated to be 4.1 at 4 weeks. The standard deviation of change in the CAFE study Berenson et al (2011) was 3.2 at 1 month. The standard deviation of change from Lane et al (2011) is estimated to be 2.4 at 1 day post-procedure. It is not known which of those studies will most closely match the population and test conditions in this study. The median of those 3 studies is 3.2. To account for this study having a longer follow-up period and a more diverse patient population, and thus more opportunity for variability, the standard deviation for our sample size calculation will be increased to 3.5.

The minimal clinically important difference (MCID) of 2 points was used to interpret pain score differences in terms of clinical relevance in Bagla et al (2016) and a clinically significant change in pain of 2 points was also identified in Greenwood (2015). This will be used for our calculations.

Bagla (2016) followed subjects for 3 months post procedure. They reported that pain scores were provided for 68% of subjects (32% not provided) at 3 months. This will be used for our calculations.

The PASS program used to calculate the sample size was the one-sample t-test power analysis, $mean_0$=0, $mean_A$=2, standard deviation (of change) =3.5, two-sided significance level (alpha)=0.05, and power=0.90. The required sample size was 35. To account for subjects getting treated but not providing the 3-Month data, the treated sample size is adjusted for a 32% loss, to 52.

A sample size of 35 subjects successfully treated and completing the pain assessment at 3 months is expected to provide results that will be considered relevant to clinicians, as well as provide acceptable power to test the primary objective.

Sample size requirements were only calculated for the primary objective. There are no sample size requirements for the secondary objective and the additional objectives.

Enrollment Sample Size

The study size will be 250 enrolled subjects. The goal is 100 with metastatic lesions involving only the vertebral body, 100 with metastatic lesions outside the vertebral body, and 50 with benign bone tumors. The increased sample size will allow for richer safety reporting and long-term follow-up.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized by study visit in a flow diagram. Discontinuations will be summarized by visit, and discontinuation reasons will be provided.

7.1.2 Clinical Investigation Plan (CIP) Deviations

CIP deviations occurring during the study will be summarized by deviation type.

7.1.3 Analysis Sets

Analysis Sets

There are 3 analysis sets:

> ***Enrolled***: all enrolled subjects. The demographics of this set, and specifically the subjects in this set but not in the Treated Analysis set, will only briefly be characterized. Otherwise, the efficacy and safety analyses will be on the following two analysis sets.

The analysis sets to be included in the efficacy analyses (primary objective, secondary objective, and additional measures) are described below.

> ***Treated Analysis Set***: all subjects who are successfully treated with the OsteoCool™ RF Ablation system.
>
> ***Completers Analysis Set***: the subset of Treated Analysis Set subjects who provided endpoint data at the 3-Month Visit. The Completers Analysis Set will be a subset of the Treated Analysis Set. The Completers Analysis Set will be the analysis population for the primary objective hypothesis testing.

The safety analyses will utilize the Treated Analysis Set.

Objective Cohorts

There will be two objective cohorts, which will be used to separate the subjects to be analyzed in the primary objective versus the secondary objective. At the time of treatment with the OsteoCool™ RF Ablation system, subjects will get assigned to one of the two cohorts depending on the lesion type(s) treated. The two cohorts encompass the entire set of Treated Analysis Set subjects and are mutually exclusive. Each objective cohort will have a Treated Analysis Set and a Completers Analysis Set.

There will be a small number of subjects that are enrolled, but do not undergo the RFA procedure. They will not be assigned to an objective cohort.

> ***Primary Objective Cohort***: subjects with metastatic lesions involving the vertebral body only
>
> ***Secondary Objective Cohort***: subjects with metastatic lesions outside the vertebral body and/or benign bone tumors. This includes subjects with a combination of lesions involving the vertebral body and outside the vertebral body. This cohort may get divided further depending on treatment site (for example: non-vertebral bone, benign bone tumors, combinations).

7.2 General Methodology

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package (e.g., SAS version 9.4 or higher) will be used to analyze the study results.

The analysis methods are provided for each objective in Section **Error! Reference source not found.**.

7.3 Center Pooling

Due to the relatively small number of subjects expected at each center, there is no plan to use statistical methods to test for a difference among centers. Primary objective results will be summarized by center to verify there is not a site that unduly influences the results, and will be included in reports if there are concerns about the center effect.

There is no plan to exclude any centers from the analysis.

For the overall study size of 250, each center can contribute no more than 50 subjects (from both subject cohorts combined) without prior Medtronic approval.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

The primary and secondary objective endpoint assessments are planned to be collected at the 3-Month follow-up visit.

Imputation of values for missing data for primary and secondary efficacy analyses will be performed as follows.

Completers Analysis Set: The Completers Analysis Set will be analyzed without imputations for missing data. (By definition, the endpoint data was provided.) Based on published data in this patient population (Bagla, 2016) it is assumed that the primary reasons for missing endpoint data will be death or inability to contact subjects due to deteriorating health and not related to pain score level. Thus, inclusion in the Completers Analysis Set is assumed to not be confounded with endpoint pain score level.

Sensitivity Analysis: The Treated Analysis Set is expected to have missing endpoint data. The frequency, timing, and reasons for missing data will be reported and analyzed to assess potential for bias. Sensitivity analyses of the primary objective, detailed in the primary objective Analysis Methods section below, will include analyzing the Treated Analysis Set using multiple imputation and single imputation.

7.5 Adjustments for Multiple Comparisons

At the time of the primary objective report, the primary objective will be tested at a two-sided alpha level of 0.05. There are no other hypothesis tests associated with the secondary objective or additional measures, so no adjustment for multiple endpoints is required.

7.6 Demographic and Other Baseline Characteristics

Demographic characteristics and baseline cancer and pain history will be summarized for all enrolled and treated subjects.

7.7 Treatment Characteristics

The RFA procedures will be summarized. The procedures will be summarized by overall procedure characteristics (procedure time, number of target sites, target site location(s), admission type, anesthesia methods, imaging guidance system) and also by individual procedure site characteristics (RFA approach, number of ablations within target site, technical success, cementoplasty performed and type, cement extravasation occurrence and clinical significance).

Concomitant therapies will be summarized by the number of subjects taking each of the treatment types, and radiation treatment characteristics.

7.8 Interim Analyses

Regular reporting of study progress and safety experience will be made in annual progress reports.

The plan for the analyses of the primary objective and the other study objectives is described earlier in Section 5 Investigation Plan.

No formal statistical interim analyses of the study objectives are planned.

7.9 Evaluation of Objectives

The primary objective hypothesis will be tested after the sample size requirements for it have been met. The sample size requirement is 35 subjects successfully treated and completing the pain assessment at 3 months. Prior to the date the 35th subject completes the 3-month visit, the visit cut-off date will be estimated for the database snapshot. If additional subjects are enrolled later and also treated for metastatic lesions involving only the vertebral body, those additional subjects will be combined with the first group and summarized together in the Final Study Report. However, no additional hypothesis testing will be performed in the Final Study Report.

7.9.1 Primary Objective

To demonstrate an improvement from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in only the thoracic and/or lumbar vertebral body(ies)

Hypothesis

H_0: $\mu_c = 0$
H_A: $\mu_c \neq 0$
Where μ_c is the mean change from baseline to the 3-Month Visit in worst-pain score.

Data Collection

At the baseline and 3-Month study visits, the worst pain question in the BPI will be used to evaluate the pain severity:

> Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours (circle only one number, 0-10). No pain = 0, Pain as bad as you can imagine = 10

Endpoint Definition

Change in pain will be calculated as:

$$\mu_c = \text{worst-pain}_{\text{3-month}} - \text{worst-pain}_{\text{baseline}}$$

A negative value for change in pain represents a lowering of the subject's pain score (an improvement, or reduction in pain) and a positive value represents an increase in the subject's pain score (a worsening, or increase in pain).

Analysis Methods

The main analysis for the primary objective hypothesis testing will be on the Primary Objective Cohort using the Completers Analysis Set.

A two-sided t-test with alpha=0.05 will be used to test the null hypothesis of no change in worst-pain score between baseline and 3 months. If the p-value is <0.05, the primary objective will be demonstrated, and statistical significance will be declared.

If the distribution of the change scores does not meet the assumption of normality, by calculating the Shapiro-Wilk W statistic probability, the non-parametric Wilcoxon signed-rank test will be used to test for significant change with alpha=0.05, two-sided. P-values less than 0.05 for the Shapiro-Wilk statistic will indicate non-normality.

In order to include all the treated subjects in the analysis, a sensitivity analysis will be performed on the Treated Analysis Set. The endpoint data will first undergo multiple imputations (MI). Rather than filling in a single value for each missing value, MI replaces each missing value with a set of "plausible" values that represent the uncertainty about the correct value to impute. These multiple imputed datasets are then analyzed using standard statistical procedures and then combined into one analysis result with an appropriately increased variance. The model variables in the MI analysis may include the following when deemed appropriate: the endpoint variable at 3 months and the endpoint variable at baseline, 3 days, 1 week, and 1 month, baseline covariates of subject age, Karnofsky score, and time from primary cancer diagnosis to baseline. The method to be used is the Markov chain Monte Carlo (MCMC) method of SAS (version 9.4 or higher). This is an iterative method that can be used when the pattern of missing data is arbitrary (monotone or non-monotone). The default number of iterations will be used (n=25) and, if needed, will be increased until the Markov chain converges. The seed will be "16075".

To allow comparison to Bagla (2016) results, a single imputation method, Last Observation Carried Forward, will also be performed, substituting the Treated Analysis Set's endpoint variable at the last available follow-up for the missing endpoint variable.

The analyses above are for the Primary Objective Report. For the Final Study Report, descriptive statistics, as well as confidence intervals, of the change in pain will be reported.

In the Primary Objective Report, the sensitivity analyses will include Treated Analysis Set subjects that have procedure dates before the last subject's procedure date in the Completers Analysis Set. In other words, subjects recently treated, but not expected to have been followed for the whole 3 months at the time of the snapshot, will not be in the sensitivity analyses.

7.9.2 Secondary Objective

To characterize change from baseline to 3 months post radiofrequency ablation in worst pain score in the past 24 hours in subjects treated for metastatic lesions in the periacetabulum, iliac crest, and/or sacrum, and for benign bone tumors

Hypothesis

There is no formal hypothesis. The objective is to characterize the change in pain.

Data Collection and Endpoint Definition

The data collection and endpoint definition are identical to the primary objective section.

Analysis Methods

The main analysis for the secondary objective will be on the Secondary Objective Cohort and will use the Completers Analysis Set.

Descriptive statistics, as well as confidence intervals, of the change in pain will be reported.

Missing data imputation and sensitivity analysis using the Treated Analysis Set will be performed similar to the primary objective methods described in Section 0.

The subsets of subjects in the Secondary Objective Cohort (subjects with metastatic lesions outside the vertebral body and/or benign bone tumors) will be reported on as a whole, and also individually (metastatic lesions outside the vertebral body, benign bone tumors, and combinations of differing lesion types.)

7.9.3 Additional Measures

7.10 Safety Evaluation

To characterize incidence of all device, procedure and/or therapy related adverse events and device deficiencies from enrollment to the 12-Month Visit.

Data Collection and Endpoint Definitions

Reported adverse events and device deficiencies will be collected on eCRFs. They will be coded and summarized using the most recent Medical Dictionary for Regulatory Affairs (MedDRA).

Adverse event relationships will be collected for the study procedure, study therapy, OsteoCool system, and any other device. Relationship strength is categorized as (in order) Not Related, Unlikely, Possible, Probable, or Causal. Adverse events will be considered as "related" if any of the Possible, Probable, or Causal categories are indicated. Deaths will be collected on the Study Exit form and the Adverse Event form if applicable. The study will utilize an independent Clinical Events Committee (CEC) to adjudicate deaths to determine the relationship of the death to the device, procedure and/or therapy.

Analysis Methods

The Treated Analysis Set will be included in the safety measures. Since adverse events were only reportable if they were related to the device, therapy and/or procedure, by definition no adverse events could occur prior to the RFA procedure. Therefore, there is no need to include the enrolled subjects not receiving the RFA procedure.

Adverse events will be presented in summary tables displaying the number of serious events, the number of events, the number of subjects with ≥1 event, and the percentage of subjects with ≥1 event. The events will be presented by MedDRA system organ class (SOC) and MedDRA preferred term (PT). The events will also be presented sorted in descending order of frequency overall. Adverse event tables will be displayed by study phase where applicable. Adverse events will be presented in aggregate as well as separated out by relationship to device, therapy and/or procedure. The analyses will also be

presented by objective cohort. Adverse events may be reported using the classification system used by the Society of Interventional Radiology.

Subject exposure will be characterized. If many subjects discontinue prematurely, the event rates may be adjusted by follow-up time.

Analyses of deaths will be presented using the final CEC determination. Any difference between CEC determination and investigator reporting will be noted in the reports.

Device deficiencies will be presented in summary tables similar to adverse events.

7.11 Changes to Planned Analysis

There are no changes to the planned analysis.

8. Validation Requirements

Statistical programming code that affects the result of the main analysis for the primary objective will be validated using Level I validation (peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer). For this study the primary objective hypothesis test will be validated using Level I validation.

Programming code that affects the result of the main analysis for the secondary objective will be validated using at least Level II validation (peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output).

In addition, those main analyses that are planned for publication will be validated with Level II validation.

Level III validation (original Statistical Programmer performs a visual inspection of the code and output to confirm functionality) may be used for any previously validated program where only minor/administrative changes were made (e.g., change the location of the data directory).

9. References

Bagla S, Sayed D, Smirniotopoulos J, et al. Multicenter Prospective Clinical Series Evaluating Radiofrequency Ablation in the Treatment of Painful Spine Metastases. Cardiovasc Intervent Radiol. 2016;39(9):1289-1297. doi:10.1007/s00270-016-1400-8.

Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol. 2011;12(3):225-235. doi:10.1016/S1470-2045(11)70008-0.

Centers for Disease Control and Prevention > Opioid Overdose > Resource Center website https://www.cdc.gov/drugoverdose/resources/data.htmlGreenwood TJ, Wallace A, Friedman MV, Hillen TJ, Robinson CG, Jennings JW. Combined Ablation and Radiation Therapy of Spinal Metastases: A Novel Multimodality Treatment Approach. Pain Physician. 2015;18(6):573-581. https://libcontent.medtronic.com:2908/pubmed/26606009.

Lane MD, Le Huy BQ, Lee S, et al. Combination radiofrequency ablation and cementoplasty for palliative treatment of painful neoplastic bone metastasis: experience with 53 treated lesions in 36 patients. Skeletal Radiol. 2011;40(1):25-32. doi:10.1007/s00256-010-1010-5.

OPuS Medical Imaging Protocol Version 1.0; 2018 01 02, Medtronic internal document